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REVIEW

Emotion recognition support system: Where physicians and psychiatrists meet linguists and data engineers

Peyman Adibi, Simindokht Kalani, Sayed Jalal Zahabi, Homa Asadi, Mohsen Bakhtiar, Mohammad Reza Heidarpour, Hamidreza Roohafza, Hassan Shahoon, Mohammad Amouzadeh

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Abstract

An important factor in the course of daily medical diagnosis and treatment is understanding patients' emotional states by the caregiver physicians. However, patients usually avoid speaking out their emotions when expressing their somatic symptoms and complaints to their non-psychiatrist doctor. On the other hand, clinicians usually lack the required expertise (or time) and have a deficit in mining various verbal and non-verbal emotional signals of the patients. As a result, in many cases, there is an emotion recognition barrier between the clinician and the patients making all patients seem the same except for their different somatic symptoms. In particular, we aim to identify and combine three major disciplines (psychology, linguistics, and data science) approaches for detecting emotions from verbal communication and propose an integrated solution for emotion recognition support. Such a platform may give emotional guides and indices to

the clinician based on verbal communication at the consultation time.

Key Words: Physician-Patient relations; Emotions; Verbal behavior; Linguistics; Psychology; Data science

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Core Tip: In the context of doctor-patient interactions, we focus on patient speech emotion recognition as a multifaceted problem viewed from three main perspectives: Psychology/psychiatry, linguistics, and data science. Reviewing the key elements and approaches within each of these perspectives, and surveying the current literature on them, we recognize the lack of a systematic comprehensive collaboration among the three disciplines. Thus, motivated by the necessity of such multidisciplinary collaboration, we propose an integrated platform for patient emotion recognition, as a collaborative framework towards clinical decision support.

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INTRODUCTION

In order to establish a therapeutic relationship between physician and patient, it is necessary to have knowledgeable practitioners in various specialties as well as an effective interaction and communication between physician and patient which starts with obtaining the patient's medical history and continues to convey a treatment plan[1,2]. Doctor-patient communication is a complex interpersonal interaction where different types of expertise and techniques are required to understand this relationship completely in verbal and nonverbal forms, especially when trying to extract emotional states and determinants during a medical consultation session[3]. Doctor-patient communication is a complex interpersonal interaction which requires an understanding of each party's emotional state. In this paper, our focus is on physicians' understanding of patients' emotions. When patients attend medical consultation, they generally convey their particular experiences of the perceived symptoms to physicians. They interpret these somatic sensations in terms of many different factors including their unique personal and contextual circumstances. Motivated by the illness experience, they generate their own ideas and concerns (emotions), leading them to seek out consultation[4-6]. Generally, patients expect and value their doctors caring for these personal aspects of their experience[7,8]. During interactions and conversations with patients, physicians should be able to interpret their emotional states, which can help build up trust between patients and them[9,10]. This will ultimately lead to better clinical outcomes. Also, identifying and recording these states will help complete patients' medical records. Many diseases that seem to have physical symptoms are, in fact, largely intertwined with psychological variables, such as functional somatic syndromes (FSS)[11]. Increasingly, physicians have realized that recognizing the psychological state of patients with FSS will be very effective in providing an appropriate treatment. For example, the ability to accurately understand sound states may help interpret a patient's pain. Thus, the presence of information about patients' mental states in their medical records is essential.

Emotion detection accuracy, *i.e.*, the ability to detect whether a patient is expressing an emotion cue, has consequences for the physician–patient relationship. The key to patient-centered care is the ability to detect, accurately identify, and respond appropriately to the patient's emotions[12-15]. Failure to detect a patient's emotional cues may give rise to an ineffective interaction between doctor and patient, which may, in turn, lead to misdiagnosis, lower recall, mistreatments, and poorer health outcomes[16,17]. Indeed, if the emotion cue is never detected, then the ability to accurately identify or respond to the emotion never comes into play. Doctors who are more aware of their patients' emotions are more successful in treating them[13]. Patients have also reported greater satisfaction with such physicians[18-22]. Recognizing the emotions and feelings of patients provides the ground for more physician empathy with patients[23,24]. The academic and medical literature highlights the positive effects of empathy on patient care[25]. In this regard, the medical profession requires doctors to be both clinically competent and empathetic toward the patients. However, in practice, meeting both needs may be difficult for physicians (especially inexperienced and unskilled ones)[26]. On the other hand, patients do not always overtly express these experiences, feelings, concerns, and ideas. Rather, they often communicate them indirectly through more or less subtle nonverbal or verbal "clues" which nevertheless contain

interesting clinical information which can be defined as "clinical or contextual clues"[27-29]**.** They do not say, ‘‘Hey doctor, I’m feeling really emotional right now; or do you know whether I’m angry or sad?’’ Thus, emotional cues are often ambiguous and subtle[30-33].

On the other hand, patients' emotional audiences (*i.e.*, physicians) are often inexperienced in detecting emotions. One of the most important problems physicians face in the development of this process is the difficulty of capturing the clues that patients offer and failing to encourage them to expose details about these feelings[34]. Research indicates that over 70% of patients’ emotional cues are missed by physicians [34]. It is unclear whether missed responses were the result from physicians detecting an emotional cue and choosing not to respond, or from failing to detect the cue in the first place. Indeed, these emotional cues present a challenge to doctors who often overlook them, as clinical information and therefore opportunities to know the patient's world are lost[34-37]. Physicians vary in their ability to recognize patients' emotions, with some being fully aware of the significance of understanding emotions and capable of identifying them. They also range from high emotional intelligence to low emotional intelligence. Another argument often heard from physicians is that they do not have time for empathy [38].

Despite the importance of such issues, this aspect remains grossly overlooked in conventional medical training. This comes from the fact that training emotion skills in medical schools is variable, lacks a strong evidence- base, and often does not include the training of emotion processing[39].

In the preceding paragraphs, four reasons were offered as to why physicians have failed to detect and interpret patients’ emotional states, and hence why we need to find a solution for this problem. These reasons could be summarized as follows. First, detecting patients’ emotions can contribute to healing them, as well as to increasing their satisfaction. Secondly, emotional cues are mostly indirectly found in patients’ speech. That is, emotional cues can be very subtle and ambiguous. Further, many physicians do not possess enough experience to detect patients’ emotions or even when they are skilled and experienced enough to do so, they do not have time to deal with it. In addition, training doctors to detect patients’ emotions has been thoroughly overlooked in routine medical training. Thus, if a solution can be found to help physicians recognize patients' emotions and psychological states, this problem can be overcome to a large extent.

One strategy is to develop and employ a technology that can provide information about the patient’s emotions, feelings, and mental states by processing their verbal and non-verbal indicators (Figure 1). In the present manuscript, we focus on verbal communication. Human speech carries a tremendous number of informative features, which enables listeners to extract a wealth of information about speakers’ identity. These features can range from linguistic characteristics through extralinguistic features to paralinguistic information, such as the speaker’s feelings, attitudes, or psychological states [40]. The psychological states (including emotions, feelings, and affections) embedded in people's speech are among the most important parts of the verbal communication array humans possess. As with other non-verbal cues, they are under conscious control much less than verbal cues. This makes speech an excellent guide to a human’s “true” emotional state even when he/she is trying to hide it.

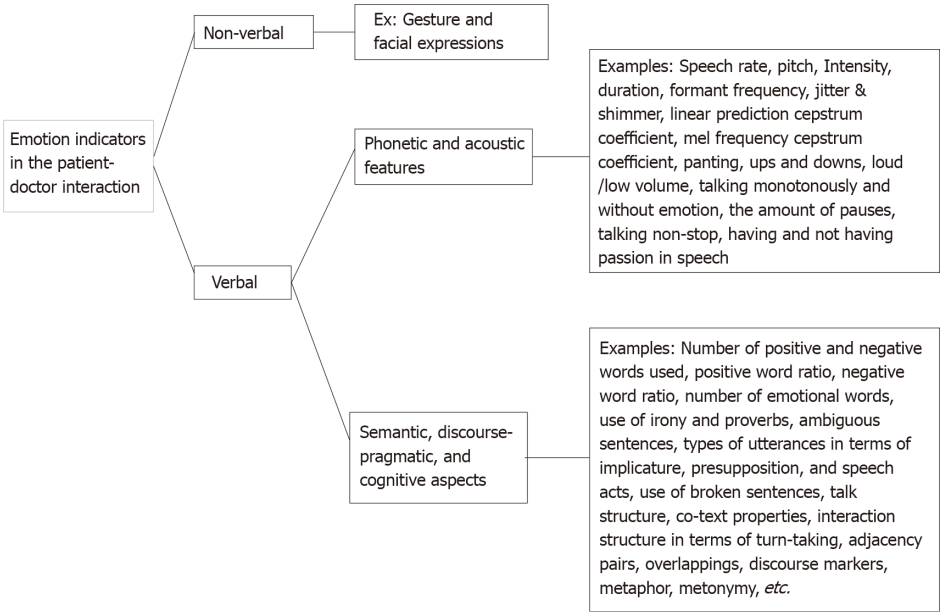
In order to design and present such technology, the first step is to know which indicators in speech can be used to identify emotions. Psychologists, psychiatrists, and linguists have done extensive research to identify people's emotions and feelings, and have identified a number of indicators. They believe that through these markers, people's emotions and feelings can be understood.

THE PSYCHOLOGICAL APPROACH

Psychologists and psychiatrists pay attention to content indicators and acoustic variables to identify people's emotions through their speech. Scholarly evidence suggests that mental health is associated with specific word use[41-43]. Psychologists and psychiatrists usually consider three types of word usage to identify emotions: (1) Positive and negative emotion words; (2) standard function word categories; and (3) content categories. They distinguish between positive (“happy”, “laugh”) and negative (“sad”, “angry”) emotion words, standard.

Function word categories (*e.g.*, self-references, first, second, and third person pronouns) and various content categories (*e.g.*, religion, death, and occupation). The frequent use of “You” and “I” suggests a different relationship between the speaker and the addressee than that of “We”. The former suggests a more detached approach, whereas the latter expresses a feeling of solidarity. Multiple studies have indicated that the frequent use of the first-person singular is associated with negative affective states[44-48], which reveals a high degree of self-preoccupation[49]. People with negative emotional states (such as sadness or depression) use second and third person pronouns less often[38-40]. These people have a lower ability to express positive emotions and express more negative emotions in their speech[44-48]. Also, people with negative emotional states use more words referring to death[44].

In addition to the content of speech, psychologists and psychiatrists also look at several acoustic variables (such as pitch variety, pause time, speaking rate, and emphasis) to detect emotions. According to the research in this area, people with negative emotional states typically have a slower speaking rate [50-54], lower pitch variety[55,56], produce fewer words[57], and have longer pauses[53,54,58].



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Figure 1 Emotion indicators in the patient-doctor interaction.

THE LINGUISTIC APPROACH

Within linguistics, various approaches (*e.g.*, phonetic, semantic, discourse-pragmatic, and cognitive) have been adopted to examine the relationship between language and emotion[56,59,60]. As far as the phonetic and acoustic studies are concerned, emotions can be expressed through speech and are typically accompanied with physiological signals such as muscle activity, blood circulation, heart rate, skin conductivity, and respiration. This will subsequently affect the kinematic properties of the articulators, which in turn will cause altered acoustic characteristics of the produced speech signals of the speakers. Studies of the effects of emotion on the acoustic characteristics of speech have revealed that parameters related to the frequency domain (*e.g.*, average values and ranges of fundamental frequency and formant frequencies), the intensity domain of speech (*e.g.*, energy, amplitude), temporal characteristics of speech (*e.g.*, duration and syllable rate), spectral features Mel frequency cepstral coefficients, and voice quality features (*e.g.*, jitter, shimmer, and harmonics-to-noise-ratio are amongst the most important acoustically measurable parameters for correlates of emotion in speech. For instance, previous studies have reported that the mean and range of fundamental frequency observed for utterances spoken in anger situations were considerably greater than the mean and range for the neutral ones, while the average fundamental frequency for fear was lower than that observed for anger[61] (Figure 2 and Table 1).

Past research has produced many important findings to indicate that emotions can be distinguished by acoustical patterns; however, there are still a multitude of challenges regarding emotional speech research. One of the major obstacles that must be tackled in the domain of emotion recognition relates to variable vocalization which exists within speakers. Voices are often more variable within the same speaker (within-speaker variability) than they are between different speakers and it is thus unclear how human listeners can recognize individual speakers' emotion from their speech despite the tremendous variability that individual voices reveal. Emotion is sensitive to a large degree of variation within a single speaker and is highly affected by factors such as gender, speakers, speaking styles, sentence structure in spoken language, culture, and environment. Thus, identifying what specific mechanisms motivate variability in acoustic properties of emotional speech and how we can overcome differences arising from individual properties remain major challenges ahead of the emotion recognition field.

With regard to investigations in the area of pragmatics (in its continental notion which encompasses discourse analysis, sociolinguistics, cognitive linguistics, and even semantics), we observe a flourishing trend in linguistics focusing on the emotion in language[59,62]. These studies have examined important issues related to referential and non-referential meanings of emotion. In semantics, the focus has been on defining emotional and sentimental words and expressions, collocations and frames of emotion[63,64], field semantics[62], as well as lexical relations including semantic extensions. However, more pragmatic and discourse-oriented studies have looked at issues in terms of emotion and cultural identity[65,66]; information structure/packaging (*e.g.* topicalization and thematicization[67] and emotion, emotive particles and interjections[68-70], emotional implicatures, and emotional illocutionary acts, deixis, and indexicality (*e.g.* proximalization and distalization[71,72], conversational analysis and emotion (*e.g.* turn-taking and interruption)[73,74], *etc.*

Table 1 Acoustic differences related to prosody and spectral features of the word (sahar) produced by a Persian female speaker in neutral and anger situations

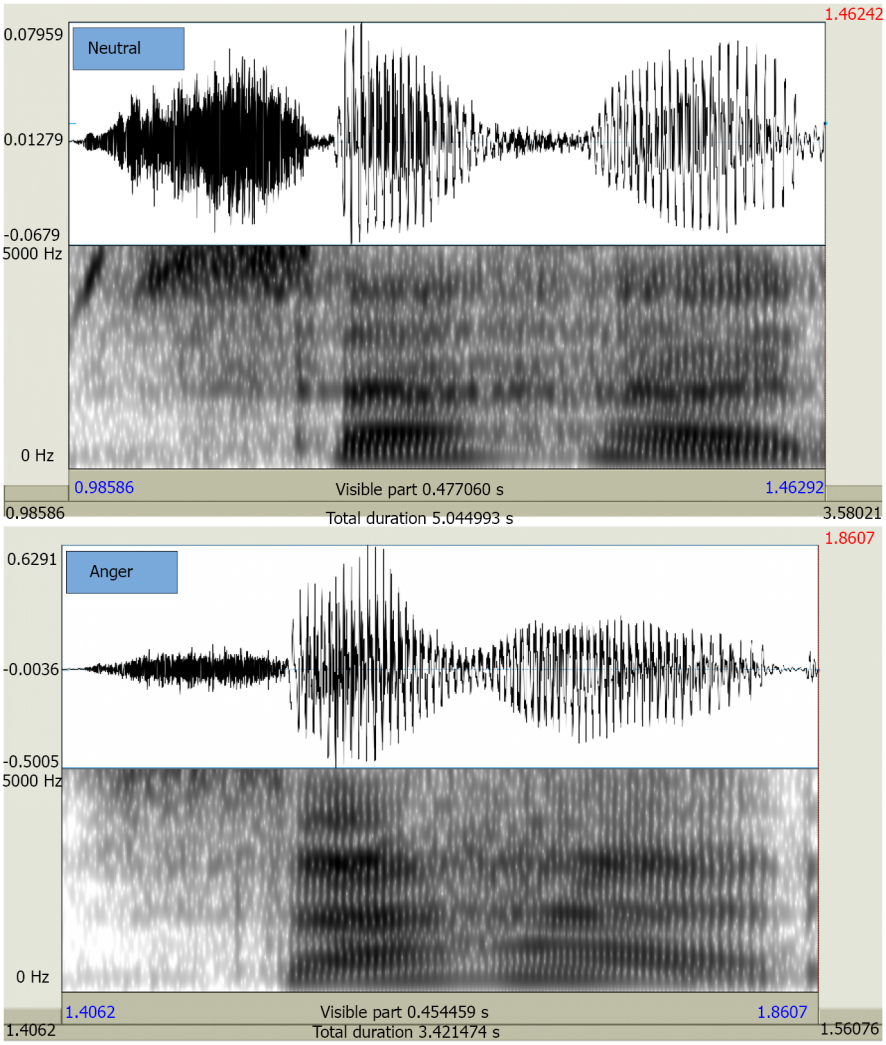
	Neutral	Angry
Prosody features		
Mean Fundamental frequency (F0)	200 Hz	225 Hz
Minimum of the fundamental frequency	194 Hz	223 Hz
Maximum of the fundamental frequency	213 Hz	238 Hz
Mean intensity	60 dB	78 dB
Spectral features		
First formant frequency (F1)	853 Hz	686 Hz
Second formant frequency (F2)	2055 Hz	1660 Hz
Third formant frequency (F3)	3148 Hz	2847 Hz
Fourth formant frequency (F4)	4245 Hz	3678 Hz

Cognitive linguists use other methods to recognize emotion in speech. The cognitive linguistic approach to emotion concepts is based on the assumption that conventionalized language used to talk about emotions is a significant tool in discovering the structure and content of emotion concepts[75]. They consider a degree of universality for emotional experience and hold that this partial universality arises from basic image schemas that emerge from fundamental bodily experiences[76-79]. In this regard, the cultural model of emotions is a joint product of (possibly universal) actual human physiology, metonymic conceptualization of actual human physiology, metaphor, and cultural context [77]. In this approach, metaphor and metonymy are used as conceptual tools to describe the content and structure of emotion concepts.

Conceptual metaphors create correspondences between two distinct domains. One of the domains is typically more physical or concrete than the other (which is thus more abstract)[76]. For example, in the Persian expression *gham dar delam* â*shiyâneh kardeh* 'sadness has nested in my heart', *gham* 'sadness' is metaphorically conceptualized as a bird and *del* 'heart/stomach' is conceived of as a nest. The metaphor focuses on the perpetuation of sadness. The benefit of metaphors in the study of emotions is that they can highlight and address various aspects of emotion concepts[75,76]. Metonymy involves a single domain, or concept. Its purpose is to provide mental access to a domain through a part of the same domain (or vice versa) or to a part of a domain through another part in the same domain[80]. Metonymies can express physiological and behavioral aspects of emotions[75]. For example, in *she was scarlet with rage*, the physiological response associated with anger, *i.e.*, redness in face and neck area, metonymically stands for anger. Thus, cognitive linguistics can contribute to the identification of metaphorical and metonymical conceptualizations of emotions in large corpora.

Although speech provides substantial information about the emotional states of speakers, accurate detection of emotions may nevertheless not always be feasible due to challenges that pervade communicative events involving emotions. Variations at semantic, pragmatic, and social-cultural levels present challenges that may hinder accurately identifying emotions *via* linguistic cues. At the semantic level, one limitation seems to be imposed by the "indeterminacy of meaning", a universal property of meaning construction which refers to "situations in which a linguistic unit is underspecified due to its vagueness in meaning"[81]. For example, Persian expressions such as *ye juriam* or *ye hâliam* roughly meaning 'I feel strange or unknown' even in context may not explicitly denote the emotion(s) the speaker intends to convey, and hence underspecify the conceptualizations that are linguistically coded. The other limitation at the semantic level pertains to cross-individual variations in the linguistic categorization of emotions. Individuals differ as to how they linguistically label their emotional experiences. For example, the expression *tu delam qoqâst* 'there is turmoil in my heart' might refer to 'extreme sadness' for one person but might suggest an 'extreme sense of confusion' for another. Individuals also reveal varying degrees of competence in expressing emotions. This latter challenge concerns the use of emotion words, where social categories such as age, gender, ethnic background, education, social class, and profession could influence the ease and skill with which speakers speak of their emotions. Since emotions perform different social functions in different social groups[82], their use is expected to vary across social groups.

Language differences are yet another source of variation in the use and expression of emotions, which presents further challenges to the linguistic identification of emotions. Each language has its own specific words, syntactic structures, and modes of expressions to encode emotions. Further, emotions are linked with cultural models and reflect cultural norms as well as values[83]. Thus, emotion words cannot be taken as culture-free analytical tools or as universal categories for describing emotions[84].



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Figure 2 Spectrograms of the Persian word (sahar) pronounced by a Persian female speaker in neutral (top) and anger (down) situations. Figure 2 shows spectrograms of the word (sahar), spoken by a native female speaker of Persian. The figure illustrates a couple of important differences between acoustic representations of the produced speech sounds. For example, the mean fundamental frequency in anger situations is higher (225 Hz) than that observed for neutral situations (200 Hz). Additionally, acoustic features such as mean formant frequencies (*e.g.* F1, F2, F3, and F4), minimum and maximum of the fundamental frequency, and mean intensity are lower in neutral situations. More details are provided in Table 1.

Patterns of communication vary across and within cultures. The link between communication and culture is provided by a set of shared interpretations which reflect beliefs, norms, values, and social practices of a relatively large group of people[85]. Cultural diversity may pose challenges to doctors and health care practitioners in the course of communicating with patients and detecting their emotions. In a health care setting, self-disclosure is seen as an important (culturally sensitive) characteristic that differentiates patients according to their degree of willingness to tell the doctor/practitioner what they feel, believe, or think[86]. Given the significance of self-disclosure and explicitness in the verbal expression of feelings in health care settings (Robinson, ibid), it could be predicted that patients coming from social groups with more indirect, more implicit, and emotionally self-restrained styles of communication will probably pose challenges to doctors in getting them to speak about their feelings in a detailed and accurate manner. In some ethnic groups, self-disclosure and intimate revelations of personal and social problems to strangers (people outside one's family or social group) may be unacceptable or taboo due to face considerations. Thus, patients belonging to these ethnic groups may adopt avoidance strategies in their communication with the doctor and hide or understate intense feelings. People may also refrain from talking about certain diseases or use circumlocutions due to the taboo or negative overtones associated with them. Further, self-restraint may be regarded as a moral virtue in some social groups, which could set a further obstacle in self-disclosing to the doctor or healthcare practitioner.

Overall, it is seen that these linguistically-oriented studies reveal important aspects of emotion in language use. In particular, they have shown how emotion is expressed and constructed by speakers in discourse. Such studies, however, are not based on multi-modal research to represent a comprehensive and unified description of emotion in language use. This means that, for a more rigorous and fine-

grained investigation, we need an integrative and cross-disciplinary approach to examining emotions in language use.

THE DATA SCIENCE APPROACH

From the data science perspective, speech emotion recognition (SER) is a machine learning (ML) problem whose goal is to classify the speech utterances based on their underlying emotions. This can be viewed from two perspectives: (1) Utterances as sounds with acoustic and spectral features (non-verbal); and (2) Utterances as words with specific semantic properties (verbal)[87-91]. While in the literature, SER typically refers to the former perspective, the latter is also important and provides a rich source of information, which can be harvested in favor of emotion recognition *via* natural language processing (NLP). Recent advances in the NLP technology allow for a fast analysis of text. In particular, word vector representations (also known as word embeddings) are used to embed words in a high dimensional space where words maintain semantic relationships with each other[92]. These vector representations, which are obtained through different ML algorithms, commonly capture the semantic relations between the words by looking into their collocation/co-occurrence in large corpora. In this way, the representation of each word and the machine's understanding of that partially reflect the essential knowledge that relates to that word, thus capturing the so-called frame semantics. The problem of SER can thus be tackled by analyzing the transcript of the speech by running various downstream tasks on the word vectors of the given speech.

As for the former perspective, different classifiers have so far been suggested for SER as candidates for a practically feasible automatic emotion recognition (AER) system. These classifiers can be put broadly into two main categories: Linear classifiers and non-linear classifiers. The main classification techniques/models within these two categories are: (1) Hidden Markov model[93-96]; (2) Gaussian mixture model[97,98]; (3) K-Nearest neighbor[99]; (4) Support vector machine[100,101]; (5) Artificial neural network[94,102]; (6) Bayes classifier[94]; (7) Linear discriminant analysis[103,104]; and (8) Deep neural network[102-107].

A review of the most relevant works within the above techniques has recently been done in[108]. We have provided a short description of the above techniques in Appendix. One of the main approaches in the last category, *i.e.*, deep neural networks, is to employ transfer learning. Recently[109] has reviewed the application of generalizable transfer learning in AER in the existing literature. In particular, it provides an overview of the previously proposed transfer learning methods for speech-based emotion recognition by listing 21 relevant studies.

The classifiers developed for SER may also be categorized in terms of their feature sets. Specifically, there are three main categories of speech features for SER: (1) The prosodic features[110-114]; (2) The excitation source features[110,111,115,116]; and (3) The spectral or vocal tract features[117-120].

Rosodic features, also known as continuous features, are some attributes of the speech sound such as pitch or fundamental frequency and energy. These features can be grouped into the following subcategories[104,105]: (1) Pitch-related features; (2) Formant features; (3) Energy-related features; (4) Timing features; and (5) Articulation features. Excitation source features, which are also referred to as voice quality features, are features which are used to represent glottal activity, such as harshness, breathiness, and tenseness of the speech signal.

Finally, spectral features, also known as segmental or system features, are the characteristics of various sound components generated from different cavities of the vocal tract system that have been extracted in different forms. The particular examples are ordinary linear predictor coefficients[117], one-sided autocorrelation linear predictor coefficients[113], short-time coherence method[114], and least squares modified Yule–Walker equations[115].

Table 2 summarizes the three discussed approaches to recognizing emotional indicators in speech 1.

Given the breadth and complexity of emotion detection indicators in psychology and linguistics, it is difficult to establish a decision support system for a doctor's emotional perception of patients. This requires a comprehensive and multidisciplinary approach. In order to build such a system, an application will be very useful. When a person experiences intense excitement, in addition to a reduction in his/her concentration, his/her mental balance is also disturbed more easily and quickly. This is also used as a strategy in sociology to take hold of people's minds.

Under unstable conditions, reasoning and logical thinking (and thus more effective and active behavior), which emerge in response to the activity of new and higher parts of the brain, are dominated by older parts of the brain, which have more biological precedents (several thousand *vs* millions of years). Thus, these older parts act impulsively or reactively.

Working in an emergency environment and sometimes even in an office has special conditions, such as excessive stress due to medical emergencies, pressure from patient companions, patient's own severe fear, as well as the impact of the phenomenon of "transference" and "countertransference" between physician and patient or between physician and patient companion. These can impair a physician's ability to reason and think logically. Thus, use of such an intelligent system can enhance doctors' efficiency, increase their awareness, and make it easier for them to manage the conditions.

Table 2 Different approaches to recognizing the emotional indicators in speech

Approaches	Emotional indicators
Psychological	(1) Positive and negative emotion words; (2) Standard function word categories; (3) Content categories; (4) The way of pronoun usage; and (5) Acoustic variables (such as pitch variety, pause time, speaking rate and emphasis)
Linguistic	(1) Phonetic: Spectral analysis, temporal analysis; (2) Semantic & Discourse-pragmatic: Words, field, cultural identity, emotional implicatures, illocutionary acts, deixis and indexicality; and (3) Cognitive: Metaphor, metonymy
Data science	(1) SER: Looking at sounds with acoustic and spectral features; and (2) NLP: Looking at words with specific semantic properties, word embedding

SER: Speech emotion recognition; NLP: Natural language processing.

THE PROPOSED SOLUTION

In the previous sections, the problem of SER was viewed from its three main perspectives: Psychology/psychiatry, linguistics, and data science, and the key elements within each perspective were highlighted. One way to integrate these three sides and benefit from their potential contributions to SER is through developing an intelligent platform. In what follows, focusing on SER in the context of doctor-patient interactions, we propose a solution for such integration.

The proposed solution consists of two key components: (1) The intelligent processing engine; and (2) The data-gathering platform.

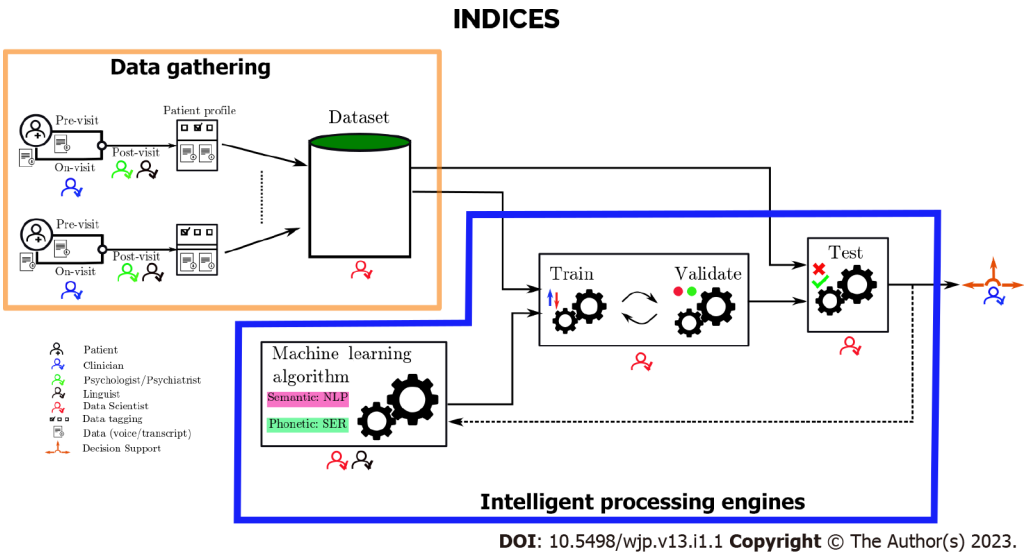
The intelligent processing engine, at the algorithmic level, is based on NLP, speech processing, and in a wider context, behavioral signal processing methods. While it is clear that the processing engine will serve as the brain of the proposed intelligent platform, and is indeed a place where the novelty, creativity, and robustness of implemented algorithms can make a great difference, it will not practically function desirably without a well-thought, flexible data-gathering platform. Thus, despite the genuine algorithms which are to be developed at the core of the platform, and the undeniable impact they will have on the performance of the system, we believe it is the data-gathering platform that will make the solution very unique. One idea is to develop a cloud-based multi-mode multi-sided data gathering platform, which has three main sides: (1) The patient side; (2) The physician side; and (3) The linguistic/psychologist side.

Regarding the functioning of the platform, three modes can be considered: (1) The pre-visit mode; (2) The on-visit mode; and (3) The post-visit mode.

The pre-visit mode will include the patient's declaration of his/her health-related complaints/conditions and concerns, which will be automatically directed to the cloud-based processing engine, and labeled *via* a SER algorithm. This mode is reinforced *via* receiving additional multi-dimensional data from the patient through filling various forms and questionnaires. Also, it is possible for the patient to submit text to accompany his/her speech. This allows one to perform additional classification/clustering tasks such as sentiment analysis or patient segmentation on the provided text, using biomedical NLP methods. The on-visit mode enables the recording of the visiting session and the clinician-patient conversations. Finally, the post-visit mode of the application provides an interface for the psychiatrist/psychologist as well as the linguist to extract and label the psychological and linguistic features within the patient's speech. Such tagging of the data by a team of specialists will in the long term lead to a rich repository of patient speech, which is of great value in training the ML algorithms in the processing engine. The proposed platform, which we have named INDICES, is depicted in Figure 3.

Although the proposed platform is to be designed such that it scales up at the population level in order to benefit from the diversity of the gathered data, it will also serve every individual as a customized personalized electronic health record that keeps track of the patient's psycho-emotional profile. As for the implementation of the platform, it is practically possible to tailor it to various devices (cell phones, tablets, PCs, and Laptops) *via* android/macOS, and web service applications

Note that emotion is essentially a multifaceted concept and no matter how sophisticated the proposed signal processing and data mining technology is, it would eventually face limitations in grasping all of its aspects. For instance, cultural aspects of expressing emotions can be a serious challenge to the technological system. Extracting the appropriate measurable features for correctly interpreting the cultural indices of emotion in speech can be a challenge, which nonetheless adds to the beauty of the problem. Further, as mentioned earlier, not all emotional indicators are embedded in the speech. Indeed, facial expressions and body gestures play important roles in expressing one's emotions as well. Hence, since the technology considered in our proposed method is focused merely on speech signals, it will of course have *blind spots* such as the visual aspects of emotion which are not exploited. This can be thought of as a main limitation that bounds the performance of the proposed emotion recognition system. However, with the same pattern that technology has always emerged throughout history, the proposed method can similarly serve as a baseline to which further improvements and additional capabilities can be added in future. We must also note that in capturing the different aspects of emotion, we are faced with



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Figure 3 Integrated platform for patient emotion recognition and decision support. It consists of the data gathering platform and the intelligent processing engines. Each patient's data, in the form of voice/transcripts is captured, labeled, and stored in the dataset. The resulting dataset feeds the machine language training/validation and test engines. The entire process of intelligent processing may iterate several times for further fine tuning. It is crucial to have collaboration among the three relevant expertise in different parts of the proposed solution.

a tradeoff between computational complexity and performance. In particular, depending on the required accuracy of the system, one may need to customize the aspects of emotion which are to be examined *via* technology, taking into account the computational burden they would impose on the system.

We shall finally end this section with two remarks. First, it is important to note that despite all integrations and optimizations involved in the design and training of the proposed intelligent platform, it would still have the intrinsic limitations of a machine as a decision-maker, some of which were mentioned above. Thus, the proposed solution would eventually serve as a decision aid/support (and not as a decision replacement). Secondly, while the proposed solution provides a global framework, it invites for a series of methodologies and solutions, which are to be adapted and customized to each language and culture setting for local use.

APPENDIX

We provide Table 3, which includes a brief description of each of the data science techniques and models mentioned earlier, along with reference sources in which further technical details of the methods can be found.

CONCLUSION

In the context of doctor-patient interactions, this article focused on patient SER as a multidimensional problem viewed from three main aspects: Psychology/psychiatry, linguistics, and data science. We reviewed the key elements and approaches within each of these three perspectives, and surveyed the relevant literature on them. In particular, from the psychological/psychiatric perspective, the emotion indicators in the patient-doctor interaction were highlighted and discussed. In the linguistic approach, the relationship between language and emotion was discussed from phonetic, semantic, discourse-pragmatic, and cognitive perspectives. Finally, in the data science approach, SER was discussed as a ML/signal processing problem. The lack of a systematic comprehensive collaboration among the three discussed disciplines was pointed out. Motivated by the necessity of such multidisciplinary collaboration, we proposed a platform named indices: An integrated platform for patient emotion recognition and decision support. The proposed solution can serve as a collaborative framework towards clinical decision support.

Table 3 A brief description of some data science models/methods

Method/Model	Short description	Ref.
HMM	A HMM is a statistical model that can be used to describe the evolution of observable events that depend on internal factors, which are not directly observable. The observed event is called a 'symbol' and the invisible factor underlying the observation is called a 'state'. A HMM consists of two stochastic processes, namely, an invisible process of hidden states and a visible process of observable symbols. The hidden states form a Markov chain and the probability distribution of the observed symbol depend on the underlying stateVia this model, the observations are modeled in two layers: One visible and the other invisible. Thus, it is useful in classification problems where raw observations are to be put into a number of categories that are more meaningful to us (Supplementary Figure 1)	[121, 122]
Gaussian mixture model	A Gaussian mixture model is a probabilistic model that assumes all data points are generated from a mixture of a finite number of Gaussian distributions with unknown parameters (Supplementary Figure 2)	[123]
KNN	KNN is a type of supervised learning algorithm used for classification. KNN tries to predict the correct class for the test data by calculating the distance between the test data and all training points. The algorithm then selects the K number of points which are closest to the test data. The KNN algorithm calculates the probability of the test data belonging to the classes of 'K' training data where the class that holds the highest probability (by majority voting) will be selected (Supplementary Figure 3)	[123]
SVM	The SVM is an algorithm that finds a hyperplane in an N-dimensional space (N: The number of features) that distinctly classifies the data points in a way that the plane has the maximum margin, *i.e.*, the maximum distance between data points of the two classes. Maximizing this margin distance would allow the future test points to be classified more accurately. Support vectors are data points that are closer to the hyperplane and influence the position as well as orientation of the hyperplane (Supplementary Figure 4)	[123]
Artificial neural network	An artificial neural network is a network of interconnected artificial neurons. An artificial neuron which is inspired by the actual neuron is modeled with inputs which are multiplied by weights, and then passed to a mathematical function which determines the activation of the neuron. The neurons in a neural network are grouped into layers. There are three main types of layers: – Input Layer – Hidden Layer(s) – Output Layer. Depending on the architecture of the network, outputs of some neurons are carried along with certain weights as inputs to some other neurons. By passing an input through these layers, the neural network finally outputs a value (discrete or continuous) which can be used to perform various classification/regression tasks. In this context, the neural network first has to learn the set of weights *via* the patterns within the so called training dataset, which is a sufficiently large set of input data labeled with their corresponding correct (expected) output (Supplementary Figure 5)	[124]
Bayes classifier	Bayes classifier, which is based on Bayes' theorem in probability, models the probabilistic relationships between the feature set and the class variable. Based on the modeled relationships, it estimates the class membership probability of the unseen example, in such a way that it minimizes the probability of misclassification	[123]
Linear discriminant analysis	Linear discriminant analysis is a method used in statistical machine learning, to find a linear combination of features that characterizes or separates two or more classes of objects or events. The resulting linear combination can be used as a linear classifier, or, as a means to dimension reduction prior to the actual classification task	[124]

HMM: Hidden markov model; KNN: K-nearest neighbor; SVM: Support vector machine.

FOOTNOTES

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ORIGINAL ARTICLE

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Evaluation of a culturally adapted cognitive behavior therapy-based, third-wave therapy manual

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Abstract

BACKGROUND

Recommendations for psychotherapy have evolved over the years, with cognitive behavioral therapy (CBT) taking precedence since its inception within clinical guidelines in the United Kingdom and United States. The use of CBT for severe mental illness is now more common globally.

AIM

To investigate the feasibility and acceptability of a culturally adapted, CBT-based, third-wave therapy manual using the Comprehend, Cope, and Connect approach with individuals from a diverse population presenting to primary and secondary healthcare services.

METHODS

A pilot study was used to assess the feasibility and acceptability of the manualised intervention. Outcome measures were evaluated at baseline, post-intervention and 12 wk-follow up. 32 participants with mental health conditions aged 20-53 years were recruited. Assessments were completed at three time points, using Clinical Outcomes in Routine Evaluation (CORE), Hospital Anxiety and Depression Scale (HADS), Bradford Somatic Inventory and World Health Organization Disability Assessment Schedule 2.0 (WHODAS). The Patient Experience Questionnaire was completed post-treatment.

RESULTS

Repeated measures of analysis of variance associated with HADS depression, F (2, 36) = 12.81, P < 0.001, partial η^2 = 0.42 and HADS anxiety scores, F (2, 26) = 9.93, P < 0.001, partial η^2 = 0.36; CORE total score and WHODAS both showed significant effect F (1.25, 18.72) = 14.98, P < 0.001, partial η^2 = 0.5. and F (1.29, 14.18) = 6.73, P < 0.001, partial η^2 = 0.38 respectively.

CONCLUSION

These results indicate the effectiveness and acceptability of the culturally adapted, CBT-based, third-wave therapy manual intervention among minoritized groups with moderate effect sizes. Satisfaction levels and acceptability were highly rated. The viability and cost-effectiveness of this approach should be explored further to support universal implementation across healthcare systems.

Key Words: Cognitive behavioral therapy; Comprehend; Cope; Connect; Ethnicity; Culture

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Core Tip: This study explores the relevance of a cultural cognitive behavioral therapy manual to manage mental health and wellbeing in primary and secondary care settings in the United Kingdom. Specificity and adaptability are key to demonstrating the relevance as well as the cost-effectiveness of mental health management approaches. Results show the effectiveness of the proposed intervention, with high levels of acceptability and participant satisfaction.

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INTRODUCTION

Cognitive behavioral therapy (CBT) was developed by Beck *et al*[1] with the aim of reducing cognitive biases and dysfunctional behaviors in order to alleviate symptoms of psychopathology. CBT was developed in an ethnocentric environment however, recent research has enabled adaptations to be made to CBT in various aspects[2]. Changes to treatment goals, assigned homework, and types of coping mechanisms taught are some of the adjustments that have been made to this intervention to make it more applicable to different psychological conditions[3,4]. Currently, adaptations to CBT to ensure relevancy and accessibility to ethnic minority groups are also being implemented such as introducing family involvement, use of appropriate language terms, and developed understanding of psychopathology from a culture viewpoint[5,6]. Social constructs and determinants play a vital role in the psychotherapies developed, driven by varying cultural factors of those within developed country-based populations. This is often identified with dysfunctions such as inadequate health policies, transparency in healthcare access and accountability mechanisms, and democratic deficits of global governance systems due to persistent global political determinants of health that have a negative impact. As such, the inclination for cultural factors and sociological constructs to influence the delivery of evidence-based therapeutics would be a logical consensus.

Few CBT adaptations employ surface changes to the intervention, which involve general and practical adaptations, such as increased awareness of cultural issues, aligning therapy with public service messages, or translating materials[7-9]. Most studies used cognitive behavioral strategies and included a variety of ethnic minority samples[6,10-15]. These studies also found that culture-specific values related to interpersonal relationships, family, and spirituality could play a significant role when providing therapy to culturally diverse patients[6,12,13,16]. Specifically, treatments that carefully accommodated cultural values resulted in improved outcomes, especially when adaptions ensured that therapy was problem-focused and direct, supports arguments that culturally diverse individuals may struggle with open-ended and non-directive therapy[17-20].

The implementation of Improving Access to Psychological Therapies (IAPT) initiatives within the United Kingdom increased the development and delivery of psychology treatments for depression and anxiety to be jointly provided with primary care services[21]. IAPT services operate through a 5-stage model, which enable adequate adjustments to be made to ensure beneficial treatment outcomes[22]. Minority ethnic groups face difficulties with accessing mental health services and it is common for them to have unfavorable experiences[23]. Hence, IAPT implemented the BAME Service User Positive Practice Guide which outlines core elements needed in IAPT service provision in order for ethnic minority groups to receive equitable treatments and outcomes[24]. One change currently active within IAPT services is ability to self-referral, removing to obstacle of organizational discrimination for many groups[24]. This has seen an increase in recovery rates from 43.8% to 50% among Black and Asian populations between Quarter 4 2015/16 and Quarter 1 2021/22 data[25]. This being said, there is still a huge gap in culturally-accommodating interventions within IAPT service provision.

Interestingly, National Health Service (NHS) Digital reported that the service users of IAPT were primarily Caucasian patients (78.2%) while only 16.4% were from ethnic minority background[26]. This may indicate a lack of acceptability of IAPT treatments in their current form and it could be argued that the accessibility of IAPT services to diverse populations may still be limited. Although these initial findings have highlighted the need for adaptation of therapy for patients from diverse ethnic minority backgrounds, concerns around the adaptation of CBT for every ethnic group have been raised from a pragmatic perspective, due to limitations within scalability and sustainability[27]. In the past few years, there has been a huge shift towards personalised mental health care services, highlighting the need to consider the individual and any interplaying factors when implementing services[27,28]. Culture is an entity which has significant effects on the psychopathology and help-seeking behavious of individuals hence should be accounted for when implementing interventions[6]. It is common for interventions and assessment tools to be translated to endless languages[29,30], and adaptations in accordance to culture should be accepted on the same terms. This being said, the translatability of interventions to other languages raises socio-economical issues for healthcare systems and policymakers alike yet, not considering translatability could exacerbate health inequality concerns and the same goes for adaptations to cultures. For these reasons, the authors developed a therapy manual that uses a generic third-wave approach, taking into consideration the above factors as well as sensitive forms of therapy in recognition of cultural bias in psychological therapies[15,23,31-35]. CBT and Comprehend, Cope, and Connect (CCC) interventions can be adapted to treat various psychological illnesses but there is also scope for these treatments to be adjusted in accordance to culture[36]. CCC has been chosen due to its universal applicability to levels of processing as it does not require specific adaptation for different ethnicities[37], and indeed the current study included individuals from African, Caribbean, South Asian, and Chinese backgrounds among others. Many Western therapies were developed through an individualistic approach but CCC lends itself to involving family and significant others within the intervention, incorporating aspects of mindfulness, spirituality, and faith. Third-wave approaches to CBT moved the focus towards interpersonal impacts on psychopathology and treatments such as relationships, values, acceptance, and beliefs[38]. Acceptance of different faiths and beliefs are equally important to ensure clinically optimal, yet culturally sensitive diagnostic and treatment approaches are rendered to all patients. Previous literature reports on the increased efficacy of third wave treatments, such as mindfulness-based cognitive therapy or acceptance and commitment therapy, compared with standard interventions across all populations and this paper aims to add to current understandings[39-41].

CCC is a third-wave cognitive behavioral approach based on a collaboratively arrived at, emotion focused, strengths based and trauma informed formulation that leads naturally to the identification of vicious cycles. It is evident at this stage that breaking the cycles is necessary, and skills such as mindfulness, arousal management and emotion management, as well as behavior change are identified and encouraged[42]. The development of the culturally adapted CBT based third-wave CCC manual offers high replicability of this study and the potential for a larger sample and introduction of a control group for comparison. High feasibility for further research using this manualized therapy is also indicated by the good recovery and retention rates, as well as positive patient experience questionnaire (PEQ) scores, which significantly indicated high levels of satisfaction and experience.

MATERIALS AND METHODS

Study design

An uncontrolled pilot study was conducted to explore the feasibility, acceptability, and effectiveness of culturally adapted, a third-wave based cognitive behavioral approach using CCC as a therapeutic intervention for patients with common mental disorders and emotional problems. The study was conducted within IAPT and secondary adult mental health services at an NHS Foundation Trust in the United Kingdom as CCC training has been implemented across both services.

Recruitment of participants

The recruitment of participants was through Community Mental Health Team (CMHT) services and IAPT's iTalk service at NHS Trust. The study was advertised through posters in CMHT and iTalk services. Recruiting participants for this study was difficult despite inclusion across both IAPT and CMHT services.

Potential participants could also contact the study therapist if they were interested in taking part. All potential participants were screened for eligibility before joining the study to ensure they met the inclusion criteria. Permission to approach potential participants was obtained from the treating clinicians. Participants who agreed to be approached were contacted and provided with an ethically approved participant information sheet. The researcher met participants in person to discuss the study in detail and obtain informed consent if interested in taking part. Participants were given a minimum of 48 h to decide if they would like to participate in the study. All participants who consented were informed that they could withdraw from the study at any time.

Eligibility

Participants with moderate to severe mental health problems were identified from IAPT services and secondary care services within the NHS Trust. Our target population was adult patients, aged 18 years and above, with moderate to severe mental illness as confirmed by specialist psychiatric services and documented in the electronic health records (F32: Depressive episode; F20: Schizophrenia; F41.1: Generalised anxiety disorder; F40.1: Social phobia; F43.1: Post-traumatic stress disorder; F42: Obsessive-compulsive disorder; F41.8: Mixed depression and anxiety). All patients from ethnic minority backgrounds were included following written informed consent. However, participants with an organic illness or a primary diagnosis of substance misuse and those experiencing acute psychotic symptoms were excluded from the study. Overall, 32 participants met the inclusion criteria and consented to take part in the study (Figure 1).

Ethics statement

The study was approved by the Health Research Authority London-Camden & Kings Cross Research Ethics Committee, reference number: 16/LO/1899.

Intervention

In terms of simultaneous interventions, CMHT patients were provided this intervention alongside standard treatment whilst IAPT patients were offered the adapted intervention. The CCC intervention was first evaluated within Acute Mental Health services[39-41] and developed for delivery in primary care IAPT services for complex cases[43]. Within primary care, the programme consisted of four individual sessions in which the collaborative emotion and trauma-focused formulation is agreed followed by a 12-wk group and skills-based interventions targeting emotion management and behaviour change (Tables 1 and 2). One or two review sessions concluded the programme. The CCC manual was culturally adapted by the authors using the cultural adaptation framework published elsewhere[23]. A full account of the intervention outlining the theory and applicability of CCC is published elsewhere[44]. Although this is aside from the focus of this study, research on acute services and CCC has also been published[43].

The adaptation facilitated the inclusion of family members and careers to be involved in the therapy; allowed for the somatic conceptualisation of emotional issues and teaching stories Spirituality and religion, where relevant, are integral to all versions of CCC. The manual developed this aspect further to meet the needs of a diverse population. In many ethnic minority cultures, the family is the nucleus within households and communities, so incorporating this core value with ensure more efficacious treatment outcomes. Families are able to provide support within therapy sessions, at home with homework tasks, but also within the wider community promoting positive outcomes for the patient and acceptance of such interventions and services in the wider community[12,14]. Similarly, ethnic minority groups hold various spiritual and religious values which greatly impact understanding of psychopathology and influence help-seeking behaviors[6,45-48]. It is important to understand these elements as they greatly impact values and beliefs, and these are the concepts of wellness explored within therapy[37]. Culturally-adapted CCC used in the current study is an abridged version of standard CCC offered in IAPT therapy at the moment.

Table 1 Comprehend, Cope, and Connect schedule of sessions

Session no	Activity
1-4	Listening; introducing the states of mind; introducing mindfulness and/or breathing
	Collaboratively creating the formulation diagram
	Negotiating goals for therapy based on what is needed to break the vicious circles
	Sharing the draft compassionate summing up letter and looking forward to what to work on through the group programme
5-12	Goals based interventions aimed at breaking the cycles. Mindfulness is the core intervention, and the following are employed as indicated by the formulation
	Arousal management, including relaxation breathing and lifestyle adjustment to reduce chronic stress
	Behavioural activation
	Emotion management includes facing, expressing and letting go of emotion self-compassion
	Aspects of self; mindfulness managed subpersonality work. Relationship management including assertiveness building a new relationship with the past
	Follow-up at 12 wk post-therapy

Table 2 Principal interventions post formulation

Intervention
Mindfulness is the core intervention; it informs the application of the others
Arousal management (relaxation breathing *etc*.)
Behavioral activation
Facing, expressing and letting go of emotion
Self-compassion
Positive anger work
Aspects of self (mindfulness managed subpersonality work)
Relationship management including assertiveness
Building a new relationship with the past

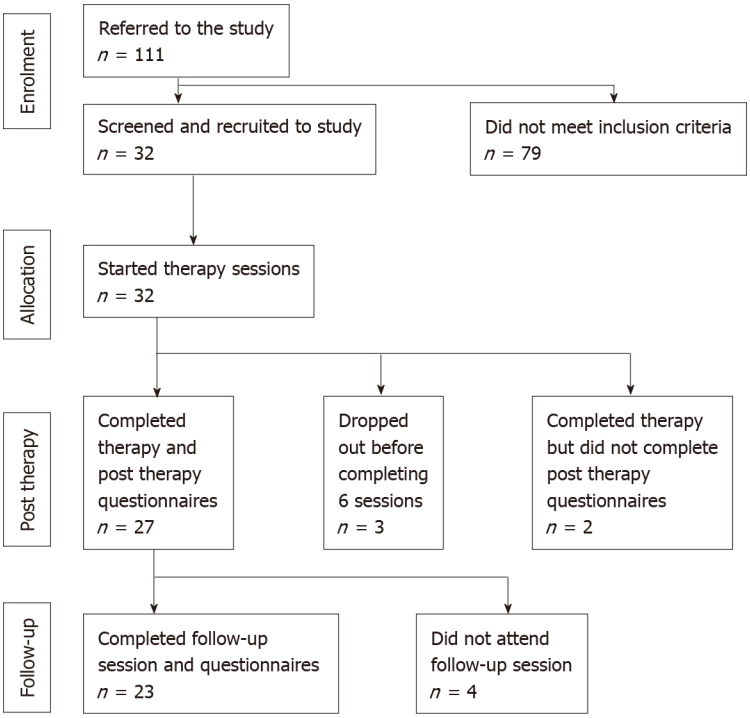
A collaborative and compassionate conceptualisation was completed within the first four sessions (Figure 2). The process starts with open-minded listening and starts with the individual's internal state and how this has been affected by recent circumstances and past adversities. The impact of the past on the present is explained. Strengths, potential values, faith, or spiritual connections are identified before the vicious cycle, representing the current management of the internal state, are tracked. Finally, a compassionate letter summing up the formulation is shared, and the intervention phase of the therapy comprises new skills to break the vicious cycles.

Modifications to the manual

Refining the manual was a key aim of the study in light of new learning arising from the challenges that emerged during therapy delivery. Adherence to the manual was monitored by an independent experienced clinician, where key cultural issues were identified and addressed accordingly. Adaptations followed the cultural adaptation framework already published elsewhere[6]. Some of the modifications included the following: (1) Allowing somatic conceptualisation of emotional challenges; (2) Managing faith issues where this impacts mental health; (3) Managing the balance between family and system expectations of the individual and their own needs; and (4) Cultural differences in attitudes to assertiveness and anger.

Outcome measures

Use of clinical outcome measures varies across primary, secondary and tertiary services. The measures used in this study were not adapted to diverse communities. This is acknowledged in the discussion section under limitations. IAPT participants in the current study also completed standard IAPT measures as this was a service requirement. The study specific outcome measures are listed below:



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Figure 1 Study Consort flow diagram.

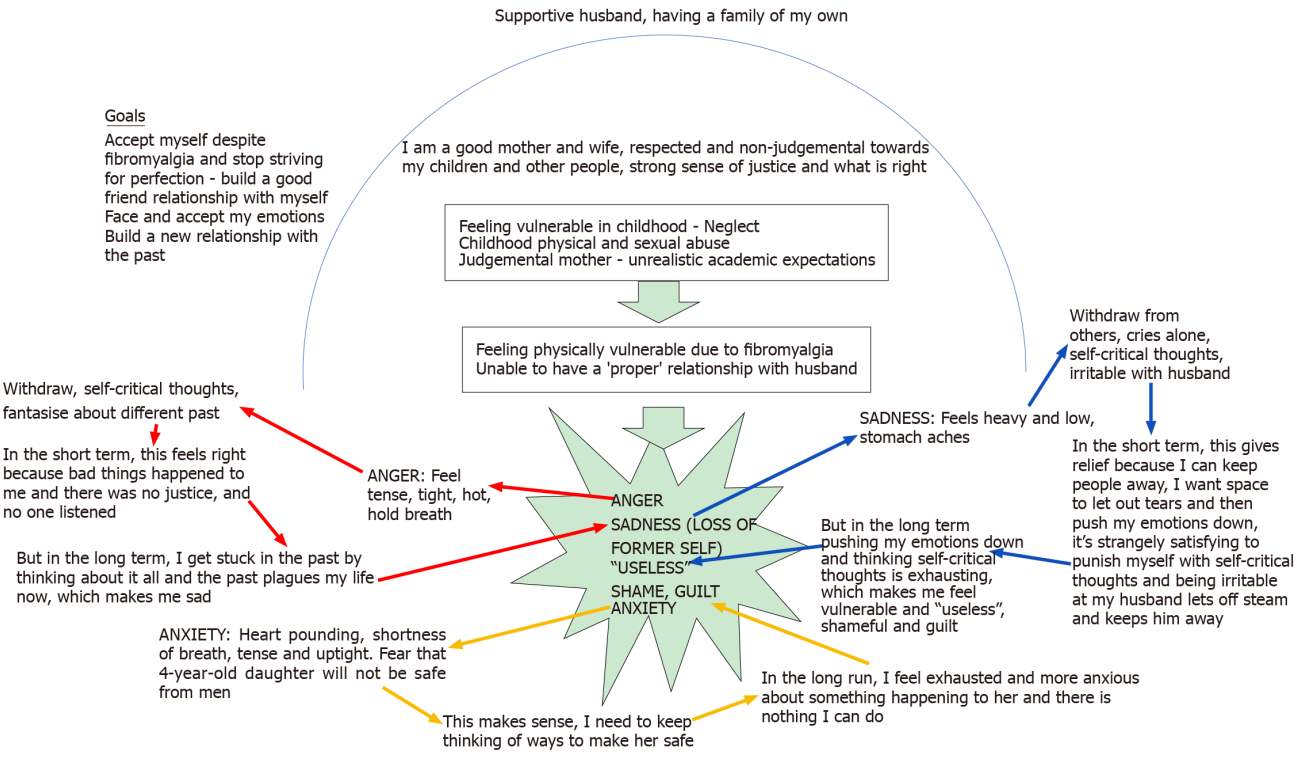


Figure 2 Jade's spikey formulation diagram. Reproduced with permission from IntechOpen. Citation: Phiri P, Clarke I, Baxter L, Elliot K, Rathod S, Naeem F. Culture Free CBT for Diverse Groups. Copyright© The Authors 2021. Published by Intechopen Publishers. The authors have obtained the permission for figure using from the Intechopen Publishers Group (Supplementary material).

Socio-demographic measures: A case report form was developed and used to collect this information from the participants. This included the following variables: Date of birth, gender, primary diagnosis, ethnicity, education, and employment history.

Hospital Anxiety and Depression scale: Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report measure of anxiety and depression. It is scored on a 4-point Likert scale. It has good internal consistency[47,48] and good concurrent validity[49].This measure was designed for a nonclinical population but has recently been validated for a mental health population and the reliability estimates have shown that the Cronbach's alpha for HADS (all items), HADS-Anxiety subscale (HADS-A) and HADS-Depression subscale (HADS-D) was 0.91, 0.90 and 0.80 respectively[45,47].

The Bradford Somatic Inventory: Bradford Somatic Inventory (BSI) is used to measure somatic symptoms. It has 45 items[50]. Scores above 21 indicate depression. It was developed from symptom reports by psychiatric patients in Pakistan and Britain with clinical diagnoses of common mental health problems. The BSI enquires about a wide range of somatic symptoms during the previous month, and if the subject has experienced a particular symptom, whether the symptom has occurred on more or less than 15 d during the month (scoring 2 or 1, respectively).

World Health Organization Disability Assessment Schedule 2.0: World Health Organization (WHO) Disability Assessment Schedule 2.0 (WHODAS) was developed by the WHO to measure disability due to physical and psychological problems and has been used extensively in research[51]. The scale covers 6 domains of functioning, including cognition, mobility, self-care, getting along, life activities, and participation. Responses are on a Likert scale of 0-4.

Clinical outcomes in Routine Evaluation: Clinical outcomes in Routine Evaluation (CORE) is a self-report questionnaire designed to be administered before and after therapy[52]. The participants were asked to respond to 34 questions about how they have been feeling over the last week, using a 5-point scale ranging from 'not at all' to 'most or all of the time'. The 34 items of the measure cover four dimensions: (1) Subjective well-being; (2) Problems/symptoms; (3) Life functioning; and (4) Risk/harm. The responses are designed to be averaged by the practitioner to produce a mean score to indicate the level of current psychological global distress (from 'healthy' to 'severe').

PEQ: Participant therapy satisfaction will be measured using the post-treatment PEQ, an 11-item self-administrated questionnaire[53]. Items 1-10 ask respondents to indicate whether their needs were met using either a two-point scale (1 being yes and 2 being no) or a five-point scale (ranging from 0 = 'not satisfied' to 5 = 'very satisfied with services'). Item 11 will capture qualitative data with any recommendations for improvement.

Statistical analysis

Frequency and descriptive commands were used to measure descriptive statistics, and an explore command was utilised to measure the normality of the data, using histograms and the Kolmorogov-Smirnov test. For each questionnaire score, an analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used. Factors used for the covariates included age, gender, diagnosis, psychiatric medication, living with someone or alone, ethnic group, having higher education or not having a partner or not, duration of mental illness, being under care of a CMHT or IAPT, history of the previous admission, use of additional services and employment status. However, because of the small sample size, these were individually entered into the analysis.

PEQ measured patient satisfaction with the intervention. It had an ordinal structure, with some items having three or more levels and others having only two levels. A correlation was carried out between PEQ and other outcome scales to investigate whether satisfaction with the intervention was related to other outcomes. Kendal's Tau was calculated where PEQ items had three or more levels, and Sommer's D was calculated where PEQ items had two levels. The statistical package IBM SPSS v20 was used to analyse the data.

RESULTS

Overall characteristics of participants

Demographic data was collected and coded between 29th March 2017 and 4th September 2019. A total of 32 participants (n = 27) female were included in the final sample. Nine participants were from Back African, Black Caribbean and Black Other ethnic groups. Thirteen participants were from either Indian, Bangladeshi, Chinese or Other Asian groups. Ten participants were from Other/Mixed groups. Baseline demographic characteristics are detailed in Table 3. It is worth noting that most participants in this study presented with a high proportion of such complexity and history of trauma (Table 4).

ANOVA results

Change in HADS depression using repeated measures ANOVA: HADS depression score was significantly different when all three time points were compared simultaneously: F (2, 36) = 12.81, P < 0.001, partial eta squared = 0.42 (Figure 3A). However, Bonferroni-adjusted pairwise comparisons

Table 3 Demographic characteristics

Characteristics	Total sample, (*n* = 32)
Gender (*n*, %)	
Male	5 (16)
Female	27 (84)
Age in years range (mean)	20-53 (34.8)
Ethnicity (*n*, %)	
Black African	2 (6)
Black Caribbean	4 (12)
Black Other	3 (9)
Indian	7 (21)
Bangladeshi	1 (3)
Chinese	3 (9)
Other Asian	2 (6)
Other/mixed	10 (32)
Diagnosis (*n*, %)	
F32: Depressive episode	12 (38)
F20: Schizophrenia	1 (3)
F41.1: Generalised anxiety disorder	9 (28)
F40.1: Social phobia	2 (6)
F43.1: Post traumatic stress disorder	2 (6)
F42: Obsessive compulsive disorder	2 (6)
F41.8: Mixed depression and anxiety	4 (13)
Setting (*n*, %)	
Community Mental Health Team	6 (19)
Improving Access to Psychological Therapies	26 (81)
Therapist delivering intervention (*n*, %)	
1	2 (6)
2	19 (60)
3	9 (28)
4	2 (6)
Number of sessions completed (*n*, %)	
12 (maximum)	19 (60)
6-11	9 (28)
Under 6	2 (6)
Unrecorded	2 (6)

showed that HADS depression significantly reduced from baseline to post-treatment and baseline to follow-up, but there was no significant difference between posttreatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

No difference between ethnic groups meant that the intervention showed similar effect in the groups (Figure 3B). However, the effect of employment status as a covariate on HADS depression was significant: F (1, 17) = 9.73, P = 0.006, eta squared = 0.36 (Figure 3C). Employed people showed lower HADS depression mean scores at all three time points. Interaction of employment with timepoint was not significant.

Table 4 Presentation information and strategies used

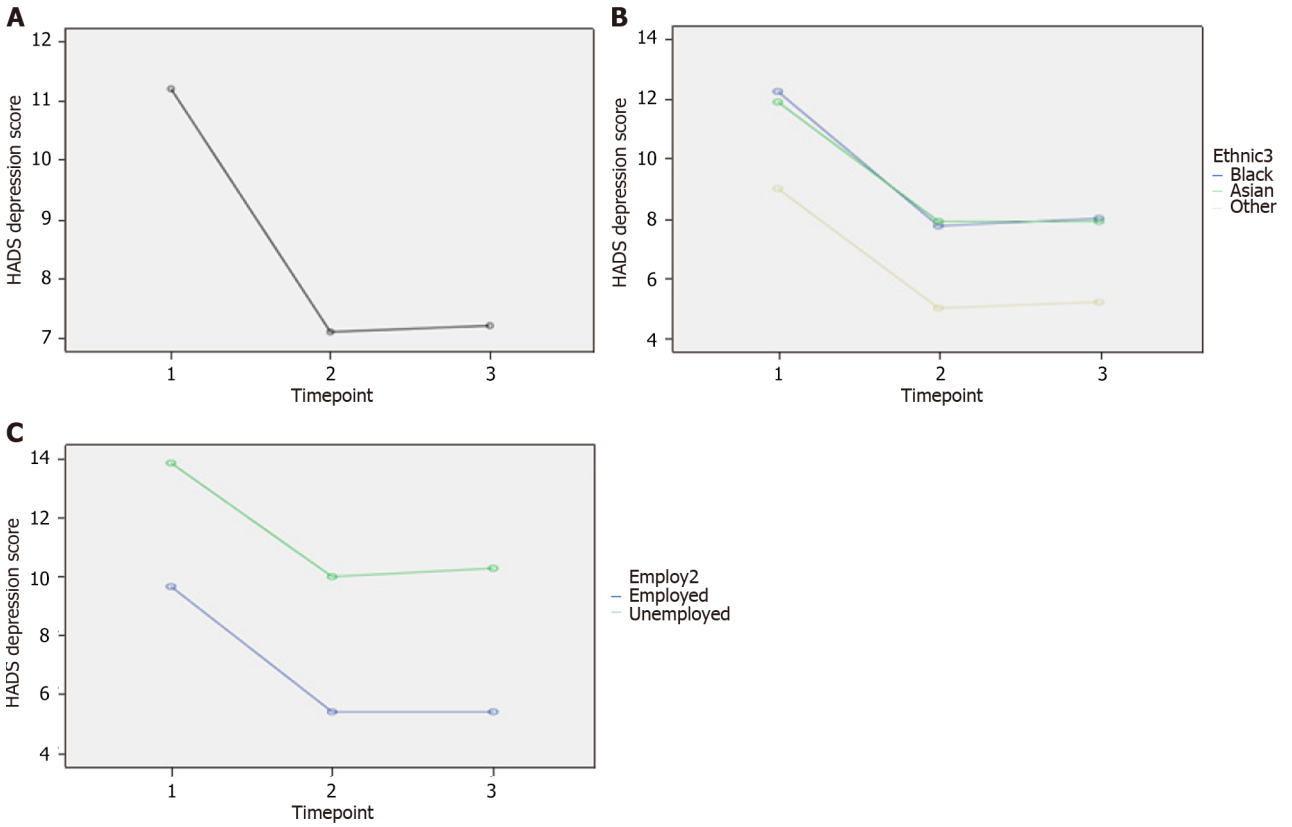
Participant	Earlier life experiences (traumatic context)	Presenting problem and impact of past	Specific CCC coping, strategies in addition to mindfulness
1	Childhood abuse (by a close family member), age 4 yr, and neglect; judgmental mother - unrealistic academic expectations	Acquiring physical disability (fibromyalgia and chronic pain), triggers sadness, anger, shame and anxiety, and feeling useless	Building a new relationship with the past: Self compassion
2	Childhood abuse. Domestic violence from partners	Anger and cannot cope when feeling unsupported, let down in the present. Unassertiveness	Building a new relationship with the past: Self-compassion; positive; anger work
3	Over-looked academically as a girl; sense of injustice. Sexual abuse by older brother told not to tell (approx 7 years old) told mother, who blamed and chastised her for the act	Unacknowledged in current family leading to disproportionate depression and anger	Emotion management; selfcom-passion
4	Punishing and neglectful mother. Anxious childhood	Inability to deal with emotions. Avoidant of relationships	Self-compassion; emotion management
5	Childhood trauma. Father nearly died in car crash when 9 years old. Family preoccupied with impact on sibling	Obsessional thoughts regarding harm to daughter. Avoidance	Arousal management; aspects of self[1]; self compassion
6	Extreme childhood fear engendered by tales of black magic	Post-natal fears for safety of son. High anxiety. Compensates with controlling pre-emptive and perfectionist behaviors	Arousal management; building a new relationship with the past; emotion management
7	Neglectful and chaotic childhood. Alcoholic father	Avoidance of emotion leading to constant activity and chronic stress. Alcohol	Arousal management; emotion management
8	Multiple deaths of family members coming close together	Obsessive health anxiety	Arousal management; self-compassion; relationship management[2]
9	Shamed within family as teen for (culturally unacceptable) homosexuality. Physical and emotional abuse by mother. Father left when 3 years old	Envy, anger, relationship and career difficulties. Loneliness copes with perfectionist ideas but behavioral inactivity (fear of failure)	Emotion management; relationship management[2]
10	Sister preferred. Sexual abuse by ex-partner. Experienced racism at work	Low self-esteem. Perfectionism leading to high stress	Positive anger work; aspects of self; relationship management
11	Childhood trauma - mother left. Sex abuse by a parent at 12 yr. Abusive childhood. Adult trauma - loss of daughter in a road traffic accident. Impact of road traffic accident - reduced memory, increased emotionality and impulse control	Flashbacks. Dissociation. Low self-esteem. Problems with emotions and relationships	Building a new relationship with the past; emotion management; relationship management[2]
12	Childhood trauma - loving family, experienced war conflict while in Turkey during Kurdish and Turkish conflict - witnessed village members being tortured by soldiers. 'Reported seeing 'Jinns', dead bodies and evil spirits' - hallucinations? Adult trauma - illegal immigrant for 14 yr - experienced extreme anxiety and feeling under attack from others	Panic, hypervigilance, avoidance of crowds and exercise	Arousal management; emotion management
13	Mental, physical and sexual abuse	Avoidance of emotion. Avoidance of intimacy	Building a new relationship with the past; relationship management[2]; emotion management; aspects of self[1]
14	Childhood sexual abuse by a parent between 5 to 12 yr. Experienced 13 yr of mental and physical abuse from husband	Emotionally overwhelmed. Withdrawal and unmotivated, or dysregulated anger	Arousal management; relationship management; self-compassion
15	Emotionally abusing and criticising childhood	Dissociation. Emotional overwhelm and relationship difficulties	Positive anger work; emotion management;self-compassion
16	Migration age 19 yr of age; hostile in-laws. Major health difficulties severely impact marriage	Suicidal and self-harm. Low mood	Arousal management; relationship management; self compassion[2]
17	Unhappy childhood; migration distress. Breast cancer	Obsessive anger at neighbours leading to conflict	Arousal management positive anger work; emotion management
18	Diagnosed with Autism. Early childhood developmental problems	Social avoidance	Arousal management; behavioral activation;

			relationship management[2]
19	Ran away from home age 11 yr. 'Kicked out' of family home at the age of 19 yr. Loss of young sibling and felt excluded	Suicidal. Avoidant of emotion	Building a new relationship with the past; self compassion; emotion management
20	Long exploitative and abusive marriage plus racial bullying at work	Stress, chronic hypertension. Relationship difficulties	Arousal management; emotion management; positive anger work; aspects of self[1]

[1]Aspects of self is mindfulness managed subpersonality work.

[2]Relationship management includes assertiveness.

Mindfulness is the core intervention; it informs the application of the others. Arousal management includes relaxation breathing and lifestyle adjustment emotion management includes facing, expressing and letting go of emotion. CCC: Comprehend, Cope, and Connect.



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Figure 3 Hospital Anxiety and Depression Scale Scores. A: Hospital Anxiety and Depression Scale (HADS)-depression scores; B: HADS-depression scores by ethnic groups; C: HADS-depression scores by employment states. HADS: Hospital Anxiety and Depression Scale.

Change in HADS anxiety using repeated measures ANOVA: HADS anxiety score was significantly different when all three time points were compared simultaneously: F (2, 36) = 9.93, $P < 0.001$, partial eta squared = 0.36 (Figure 4). However, Bonferroni-adjusted pairwise comparisons showed that HADS anxiety significantly reduced from baseline to post-treatment and baseline to follow-up, but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

Change in WHO disability scale using repeated measures ANOVA: WHO disability scale was significantly different when all three time points were compared simultaneously: F (1.29, 14.18) = 6.73, $P < 0.016$, partial eta squared = 0.38 (Figure 5A). However, Bonferroni-adjusted pairwise comparisons showed that the WHO disability scale significantly reduced from baseline to post-treatment and baseline to follow-up, but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up. However, the effect of living alone as covariate on WHO disability scale was significant: F (1, 10) = 8.99, $P = 0.013$, eta squared = 0.47 (Figure 5B). Those who were living alone had higher mean score at all three times. Interaction of living with timepoint was not significant. In addition, the effect of

Table 5 Results of repeated measures analysis of variance for outcome variables

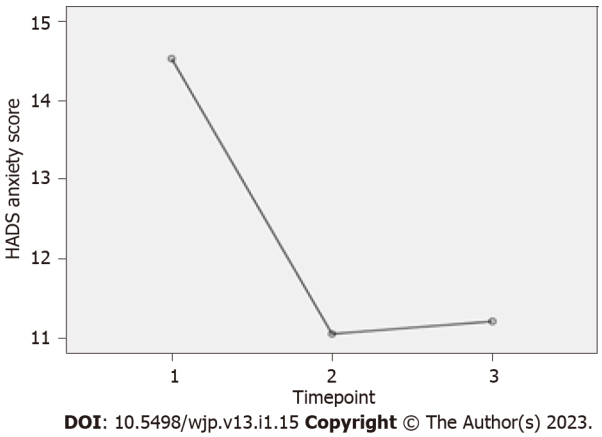
Dependent variable	Independent variable	Degrees of freedom	F value	*P* value	Partial eta squared (variance explained; *i.e.*, effect size)	Bonferroni adjusted pairwise comparisons		
HADS depression	Timepoint (within subjects)	2, 36	12.81	< 0.001	0.42	Baseline (mean 11.21 SD 4.28) *vs* post-treatment (mean 7.11, SD 3.99), *P* = 0.004	Baseline *vs* follow-up (mean 7.21, SD 4.99), *P* = 0.001	Post treatment *vs* follow-up, *P* = 1.0
	Employment (between subjects)	1, 17	9.73	0.006	0.36	Employed *vs* unemployed mean difference[1] -4.55 (95%CI: -7.62 to -1.47); employed have lower mean score at all three time points		
	Employment X time point (within subjects)	2, 34	0.06	0.94	0.004	NA	NA	NA
HADS Anxiety	Timepoint (within subjects)	2, 36	9.93	< 0.001	0.36	Baseline (mean 14.53 SD 4.01) *vs* post-treatment (mean 11.05, SD 3.40), *P* = 0.003	Baseline *vs* follow-up (mean 11.21, SD 4.05), *P* = 0.001	Post treatment *vs* follow-up, *P* = 0.831
WHO disability scale total	Timepoint (within subjects)	1.29, 14.18[2]	6.73[2]	0.016	0.38[2]	Baseline (mean 66.58 SD 40.13) *vs* post-treatment (mean 44.42, SD 32.35), *P* = 0.034	Baseline *vs* follow-up (mean 38.75, SD 26.499), *P* = 0.014	Post treatment *vs* follow-up, *P* = 0.194
	Living alone (between subjects)	1, 10	8.99	0.013	0.47	Living alone *vs* with someone mean difference[1] 51.9 (95%CI: 13.33 to 90.47); living alone have higher score at all three timepoints		
	Living alone X timepoint (within subjects)	1.21, 12.07[2]	0.39[2]	0.581	0.04[2]	NA	NA	NA
	Employment (between subjects)	1, 10	8.68	0.015	0.47	Employed *vs* unemployed mean difference[1] -44.26 (95%CI: -77.62 to -10.79); employed have lower mean score at all three time points		
	Employment X Time point (within subjects)	1.32, 13.18[2]	2.99[2]	0.1	0.23[2]	NA	NA	NA
CORE total	Timepoint	1.25, 18.72[2]	14.98[2]	0.001	0.5[2]	Baseline (mean 76.81, SD 23.26) *vs* post-treatment (mean 49.25, SD 27.00), *P* = 0.002	Baseline *vs* follow-up (mean 52.19, SD 25.72), *P* < 0.001	Post treatment *vs* follow-up, *P* = 0.404
CORE total mean with risk	Timepoint	1.25, 18.72[2]	14.98[2]	0.001	0.5[2]	Baseline (mean 2.26, SD 0.68) *vs* post-treatment (mean 1.45, SD 0.79), *P* = 0.002	Baseline *vs* follow-up (mean 1.53, SD 0.76), *P* < 0.001	Post treatment *vs* follow-up, *P* = 0.404
CORE Total mean without risk	Timepoint	1.24, 18.66[2]	16.58	< 0.001	0.53[2]	Baseline (mean 2.62, SD 0.71) *vs* post-treatment (mean 1, SD 0.87), *P* = 0.001	Baseline *vs* follow-up (mean 1.77, SD 0.79), *P* < 0.001	Post treatment *vs* follow-up, *P* = 0.523
CORE risk mean	Timepoint	2, 36	1.83	0.175	0.09	Baseline (mean 0.48, SD 0.75) *vs* post-treatment (mean 0.26, SD 0.55), *P* = 0.109	Baseline *vs* follow-up (mean 0.39, SD 0.77), *P* = 0.418	Post treatment *vs* follow-up, *P* = 0.096
CORE symptoms mean	Timepoint	2, 32	91.10	< 0.001	0.54	Baseline (mean 2.81, SD 0.77) *vs* post-treatment (mean 1.76, SD 1.03), *P* < 0.001	Baseline *vs* follow-up (mean 1.91, SD 0.89), *P* < 0.001	Post treatment *vs* follow-up, *P* = 0.317
CORE functioning mean	Timepoint	1.25, 19.92[2]	7.26	0.01	0.31	Baseline (mean 2.25, SD 0.88) *vs* post-treatment (mean 1.61, SD 0.86), *P* = 0.016	Baseline *vs* follow-up (mean 1.65, SD 0.83), *P* = 0.009	Post treatment *vs* follow-up, *P* = 0.692
CORE well being mean	Timepoint	2, 36	20.41	< 0.001	0.53	Baseline (mean 2.82, SD 0.67) *vs* post-treatment (mean 1.68, SD 0.68), *P* < 0.001	Baseline *vs* follow-up (mean 1.76, SD 0.87), *P* < 0.001	Post treatment *vs* follow-up, *P* = 0.61

BSI total	Timepoint	2, 36	6.50	0.008	0.26	Baseline (mean 22.11, SD 11.40) *vs* post-treatment (mean 19.05, SD 10.23), $P < 0.066$	Baseline *vs* follow-up (mean 16.47, SD 11.10), $P < 0.008$	Post treatment *vs* follow-up, $P = 0.041$

[1]This is the difference in average means across all three time-points.

[2]Greenhouse-Geisser value given due to significant Mauchly's test of sphericity.

CI: Confidence interval; NA: Not available; WHO: World Health Organization; CORE: Clinical Outcomes in Routine Evaluation; HADS: Hospital Anxiety and Depression Scale; BSI: Bradford Somatic Inventory.



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Figure 4 Hospital Anxiety and Depression Scale Anxiety Scores. HADS: Hospital Anxiety and Depression Scale.

employment status as a covariate on WHO disability scale was significant, F (1, 10) = 8.68, $P = 0.015$, eta squared = 0.47 (Figure 5C). Employed people showed lower WHO disability scale mean score at all three time points. Interaction of employment with timepoint was not significant.

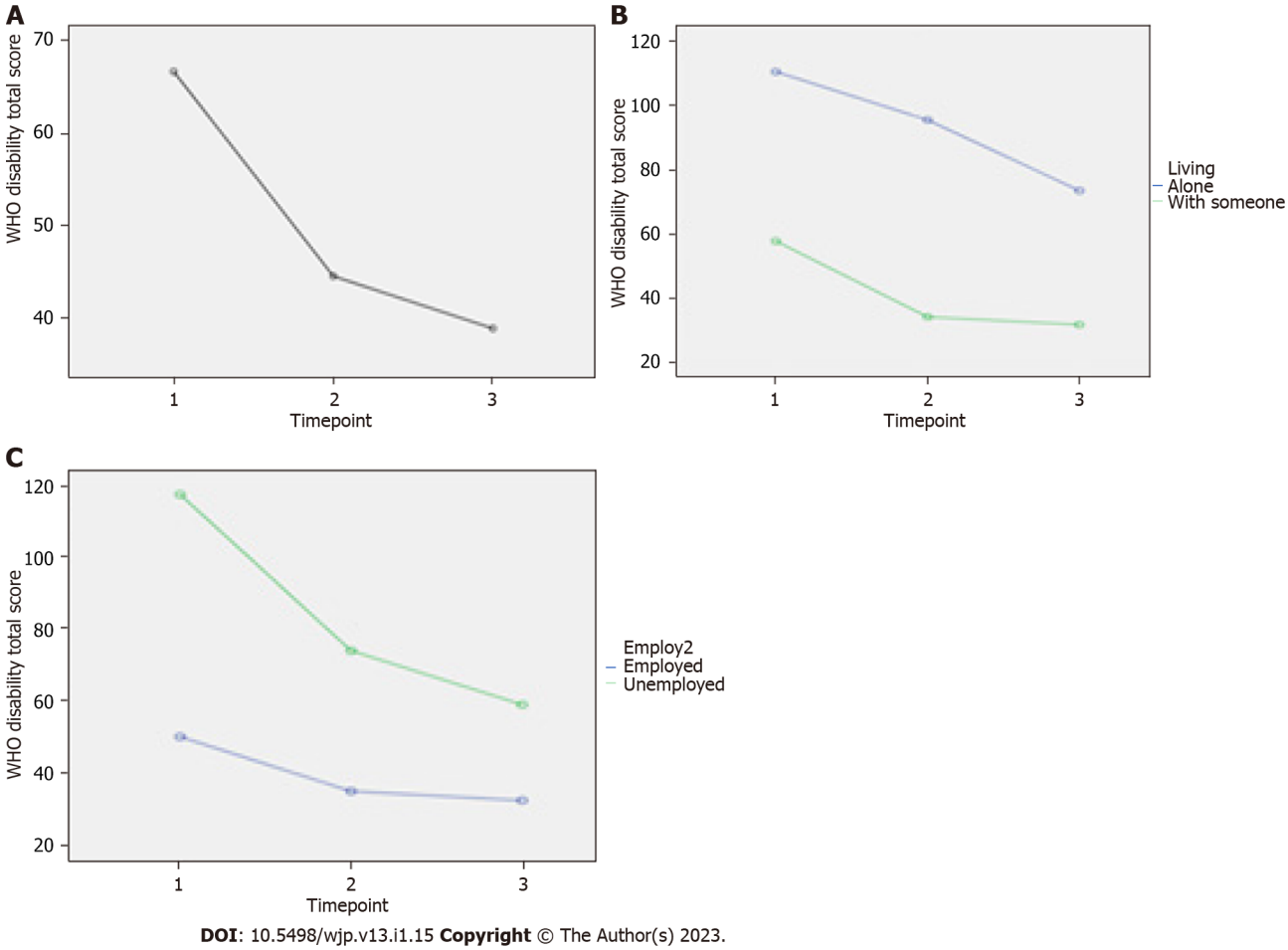
Change in CORE total score using repeated measures ANOVA: The CORE total score was significantly different when all three time points were compared simultaneously: F (1.25, 18.72) = 14.98, $P = 0.001$, partial eta squared = 0.5 (Figure 6A). However, Bonferroni-adjusted pairwise comparisons showed that CORE total score significantly reduced from baseline to post-treatment and baseline to follow-up, but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

Change in CORE total mean to risk using repeated measures ANOVA: The CORE total mean with risk was significantly different when all three time points were compared simultaneously: F (1.25, 18.72) = 14.98, $P = 0.001$, partial eta squared = 0.5. However, Bonferroni-adjusted pairwise comparisons showed that the CORE total mean with risk significantly reduced from baseline to post-treatment and baseline to follow-up; but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

The effect of the following covariates on the HADS, WHODAS, and CORE total mean with risk was not significant: Age, gender, diagnosis, psychiatric medication, living with someone or alone, ethnic group, having higher education or not, having a partner or not, duration of mental illness, being under care of CMHT or IAPT, history of previous admission, use of additional services and employment status. No difference between ethnic groups meant that the intervention showed similar effects in the groups.

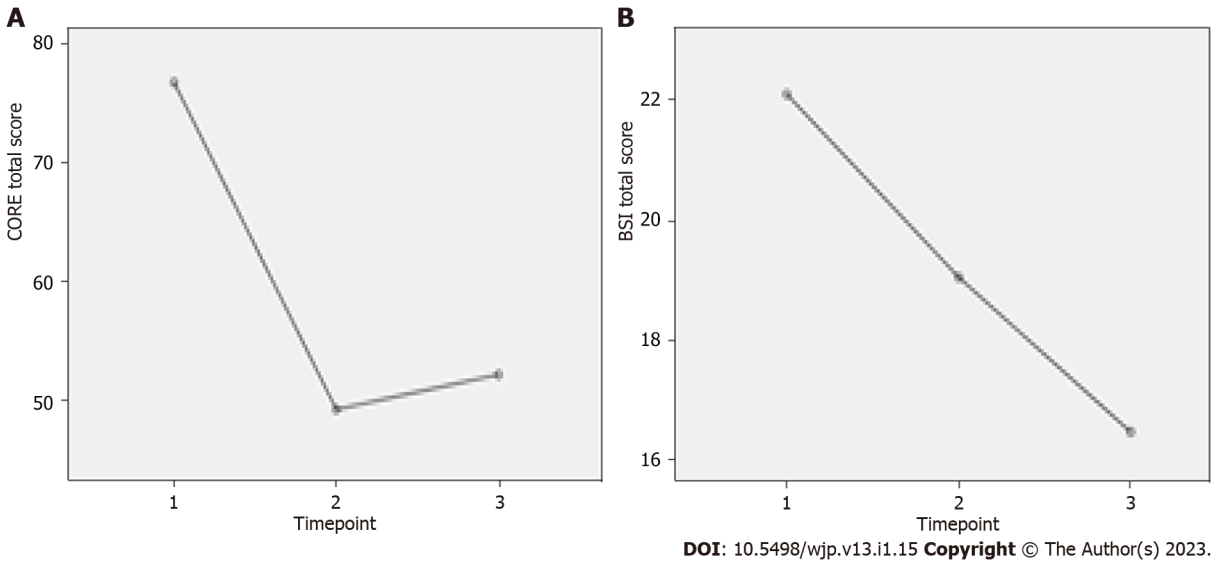
Change in CORE total mean without risk using repeated measures ANOVA: The CORE total mean without risk was significantly different when all three time points were compared simultaneously: F (1.24, 18.66) = 16.58, $P < 0.001$, partial eta squared = 0.53. However, Bonferroni-adjusted pairwise comparisons showed that the CORE total mean without risk significantly reduced from baseline to post-treatment and baseline to follow-up; but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

Change in CORE risk mean using repeated measures ANOVA: The CORE risk mean was not significantly different when all three time points were compared simultaneously: F (2, 36) = 11.83, $P = 0.175$, partial eta squared = 0.09. Furthermore, Bonferroni-adjusted pairwise comparisons showed that the CORE risk mean was not significantly different in any of the three-way comparisons (Table 5). This



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Figure 5 World Health Organization Disability Assessment Schedule 2.0 scores. A: World Health Organization Disability Assessment Schedule 2.0 (WHODAS) scores; B: WHODAS scores by living status; C: WHODAS scores by employment status. WHO: World Health Organization.



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Figure 6 Clinical Outcomes in Routine Evaluation and Bradford Somatic Inventory scores at three timepoints. A: Clinical Outcomes in Routine Evaluation; B: Bradford Somatic Inventory scores. CORE: Clinical Outcomes in Routine Evaluation; BSI: Bradford Somatic Inventory.

meant that this measurement did not change significantly between the three time points. Thus, no covariates were entered in this analysis.

Change in CORE symptoms mean using repeated measures ANOVA: The CORE symptom mean was significantly different when all three time points were compared simultaneously: F (2, 32) = 91.10, P < 0.001, partial eta squared = 0.54. However, Bonferroni-adjusted pairwise comparisons showed that the CORE symptom mean significantly reduced from baseline to post-treatment and baseline to follow-up; but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

Changes in CORE functioning mean using repeated measures ANOVA: The CORE functioning mean was significantly different when all three time points were compared simultaneously: F (1.25, 91.92) = 7.26, P = 0.01, partial eta squared = 0.31. However, Bonferroni-adjusted pairwise comparisons showed that the CORE functioning mean significantly reduced from baseline to post-treatment and baseline to follow-up; but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

Changes in CORE wellbeing mean using repeated measures ANOVA: CORE wellbeing mean was significantly different when all three time points were compared simultaneously, F (2, 36) = 20.41, P = 0.01, partial eta squared = 0.53. However, Bonferroni-adjusted pairwise comparisons showed that CORE wellbeing mean significantly reduced from baseline to post-treatment and baseline to follow-up; but there was no significant difference between post-treatment and follow-up (Table 5). This meant that there was a benefit at post-treatment and that the benefit was maintained at follow-up.

Change in BSI total using repeated measures ANOVA: The BSI total was significantly different when all three time points were compared simultaneously: F (2, 36) = 6.50, P = 0.008, partial eta squared = 0.26 (Figure 6B). However, Bonferroni-adjusted pairwise comparisons showed that the BSI total did not reduce significantly from baseline to post-treatment and but did so from baseline to follow-up; there was also a significant difference between post-treatment and follow-up (Table 5). This meant that there was no benefit at post-treatment but there was at follow-up.

ANCOVA results

Compared with ANOVA, ANCOVA further analysed the outcomes adjusted by certain covariates. This allowed us to examine the sensitivity of the findings in ANOVA towards certain covariates. If the significant results in ANOVA changed tremendously to unsignificant, the reliability of the results in ANOVA should be doubted. Such covariates could be influencing the outcomes in an undetected way and thereby contribute to the differences between groups. Therefore, we further analysed the significant model in ANOVA. After adding covariates, the P-value in ANOVA changed from less than 0.05 to larger than 0.05 in ANCOVA, thus these covariates were the key variables we should pay attention to. If the significant results in ANOVA remained significant in ANCOVA, *i.e.*, no drastic changes in the P-value, it would consolidate our finding in ANOVA by evidencing the insensitivity of the result towards the covariate.

Change in HADS depression using mixed factorial ANCOVA: With Timepoint and Employment being factor, HADS depression score adjusted by gender was not significantly different when all three time points were compared simultaneously: F (2, 42) = 0.158, P = 0.855. Also, when adjusted by age, HADS depression score did not show significant difference across three time points: F (2.42) = 0.595, P = 0.556 (Table 6). This suggested part of the differences of HADS depression scores across three timepoints could be explained by gender. Bonferroni-adjusted pairwise comparisons had the similar results to those of ANOVA.

In addition to this, other covariates, such as psychiatric medication, living with someone or alone, having higher education or not, having a partner or not, duration of mental illness, being under care of a CMHT or IAPT, history of previous admission and use of additional services, didn't change the results of the ANOVA analysis. Therefore, with factors living alone and employment, differences in questionnaire scores at three timepoints were not caused by these covariates.

Change in HADS anxiety using repeated measures ANCOVA: Results in ANOVA showed that HADS anxiety score was significantly different through three timepoints with a P-value less than 0.001 (Table 6). While HADS anxiety score adjusted by gender was not significantly different when all three time points were compared simultaneously: F (2, 44) = 0.014, P = 0.986 (Table 6). This suggested part of the difference of HADS anxiety score across three time points could be explained by gender. Bonferroni-adjusted pairwise comparison kept the similar results with those of ANOVA analysis.

Change in WHO disability scale using mixed factorial ANCOVA: Based on the results of ANOVA, model with factors employment and living alone had a P-value of 0.016 between three timepoints (Table 6). In ANCOVA analysis, with the same two factors, WHO disability scale adjusted by gender was not significantly different when all three time points were compared simultaneously: F (1.24, 22.38) = 0.354, P = 0.704 (Table 6). This meant that part of the difference of WHO disability scale across three time points could be explained by gender. With the same factors, using covariates age or higher education respectively resulted in a small increase in the P-value of time-point: From P = 0.016 (Table 5)

Table 6 Results of repeated measures analysis of covariance for outcome variables

Dependent variable	Covariate	Independent variable	Degrees of freedom	F value	*P* value	Bonferroni adjusted pairwise comparisons		
HADS depression	Gender	Timepoint (within subjects)	2, 42	0.158	0.855	Baseline (mean 11.77 SD 0.78) *vs* post-treatment (mean 7.75, SD 0.73), *P* = 0.003	Baseline *vs* follow-up (mean 7.55, SD 0.89), *P* < 0.001	Post treatment *vs* follow-up, *P* = 1.0
		Employment (between subjects)	1, 21	9.788	0.005	Employed *vs* unemployed mean difference[1] -3.96 (95%CI: -6.60 to -1.33); employed have lower mean score at all three time points		
	Age	Timepoint (within subjects)	2, 42	0.595	0.556	Baseline (mean 11.85 SD 0.77) *vs* post-treatment (mean 7.78, SD 0.74), *P* = 0.002	Baseline *vs* follow-up (mean 7.62, SD 0.89), *P* < 0.001	Post treatment *vs* follow-up, *P* = 1.0
		Employment (between subjects)	1, 21	11.266	0.003	Employed *vs* unemployed mean difference[1] -4.33 (95% CI: -7.02 to -1.65); employed have lower mean score at all three time points		
HADS Anxiety	Gender	Timepoint (within subjects)	2, 44	0.014	0.986	Baseline (mean 14.54 SD 0.77) *vs* post-treatment (mean 10.33, SD 0.75), *P* < 0.001	Baseline *vs* follow-up (mean 10.38, SD 0.86), *P* < 0.001	Post treatment *vs* follow-up, *P* = 1.0
WHO disability scale total	Gender	Timepoint (within subjects)	1.24, 22.38[2]	0.354[2]	0.704[2]	Baseline (mean 85.32 SD 8.72) *vs* post-treatment (mean 65.83, SD 7.42), *P* = 0.143	Baseline *vs* follow-up (mean 53.59, SD 8.26), *P* = 0.014	Post treatment *vs* follow-up, *P* = 0.016
		Living alone (between subjects)	1, 18	8.288	0.010	Living alone *vs* with someone mean difference[1] 37.82 (95%CI: 10.22 to 65.42); living alone have higher score at all three timepoints		
		Employment (between subjects)	1, 18	10.674	0.004	Employed *vs* unemployed mean difference[1] -30.52 (95%CI: -50.14 to -10.89); employed have lower mean score at all three time points		
	Age	Timepoint (within subjects)	1.25, 22.41[2]	3.631[2]	0.062[2]	Baseline (mean 84.69 SD 8.62) *vs* post-treatment (mean 65.47, SD 6.89), *P* = 0.138	Baseline *vs* follow-up (mean 53.30 SD 7.41), *P* = 0.011	Post treatment *vs* follow-up, *P* = 0.013
		Living alone (between subjects)	1, 18	8.167	0.010	Living alone vs with someone mean difference[1] 34.92 (95%CI: 9.25 to 60.59); living alone have higher score at all three timepoints		
		Employment (between subjects)	1, 18	14.555	0.001	Employed *vs* unemployed mean difference[1] -35.13 (95%CI: -54.47 to -15.78); employed have lower mean score at all three time points		
	Higher Education	Timepoint (within subjects)	1.22, 20.78[2]	3.506[2]	0.068[2]	Baseline (mean 84.60 SD 8.89) *vs* post-treatment (mean 65.38, SD 7.64), *P* = 0.165	Baseline *vs* follow-up (mean 52.48, SD 8.31), *P* = 0.014	Post treatment *vs* follow-up, *P* = 0.008
		Living alone (between subjects)	1, 17	7.318	0.015	Living alone *vs* with someone mean difference[1] 36.75 (95%CI: 8.09 to 65.41); living alone have higher score at all three timepoints		
		Employment (between subjects)	1, 17	10.370	0.005	Employed *vs* unemployed mean difference[1] -31.02 (95%CI: -51.34 to -10.70); employed have lower mean score at all three time points		
CORE total	Gender	Timepoint	1.47, 32.30[2]	0.028[2]	0.938[2]	Baseline (mean 73.88, SD 4.56) *vs* post-treatment (mean 47.42, SD 5.11), *P* < 0.001	Baseline *vs* follow-up (mean 48.04, SD 5.25), *P* < 0.001	Post treatment *vs* follow-up, *P* = 1.0
	Age	Timepoint	1.47, 32.23[2]	0.975[2]	0.364[2]	Baseline (mean 73.88, SD 4.48) *vs* post-treatment (mean 47.42, SD 4.95), *P* < 0.001	Baseline *vs* follow-up (mean 48.04, SD 5.15), *P* < 0.001	Post treatment *vs* follow-up, *P* = 1.0
BSI total	Age	Timepoint	2, 46	0.285	0.753	Baseline (mean 22.64, SD 2.06) *vs* post-treatment (mean 18.60, SD 2.06), *P* = 0.041	Baseline *vs* follow-up (mean 16.60, SD 2.09), *P* = 0.001	Post treatment *vs* follow-up, *P* = 0.406
	Gender	Timepoint	2, 46	1.027	0.366	Baseline (mean 22.64, SD 2.03) *vs* post-treatment (mean 18.60, SD 2.09), *P* = 0.026	Baseline *vs* follow-up (mean 16.60, SD 2.07), *P* = 0.001	Post treatment *vs* follow-up, *P* = 0.411
	Higher education	Timepoint	2, 44	2.811	0.071	Baseline (mean 22.58, SD 2.19) *vs* post-treatment (mean 18.21, SD 2.15), *P* =	Baseline *vs* follow-up (mean 16.75, SD 2.11), *P* = 0.003	Post treatment *vs* follow-up, *P* = 0.661

					0.028			
	Marital status	Timepoint	2, 46	3.146	0.052	Baseline (mean 22.64, SD 2.05) *vs* post-treatment (mean 18.60, SD 2.08), P = 0.040	Baseline *vs* follow-up (mean 16.60, SD 2.08), P = 0.002	Post treatment *vs* follow-up, P = 0.434

[1]This is the difference in average means across all three time-points.

[2]Greenhouse-Geisser value given due to significant Mauchly's test of sphericity.

CI: Confidence interval; NA: Not available; WHO: World Health Organization; CORE: Clinical Outcomes in Routine Evaluation; HADS: Hospital Anxiety and Depression Scale; BSI: Bradford Somatic Inventory.

to P = 0.062 and P = 0.068 (Table 6). It was evident from the results that the changes to the WHO disability scale between three time points was not easily explained by age or higher education. Bonferroni-adjusted pairwise comparison failed to show significant reduction of the WHO disability scale from baseline to post-treatment. However, our results showed a significant reduction of the WHO disability scale from baseline to follow-up and from post-treatment to follow-up.

Change in CORE total score using repeated measures ANCOVA: The CORE total score adjusted by gender and age respectively was not significantly different when all three time points were compared simultaneously: F (1.47, 32.30) = 0.028, P = 0.938 and F (1.47, 32.23), P = 0.364 (Table 6). After adding these two covariates respectively, the differences of scores between three timepoint were not that much, which suggested part of the difference of CORE total score across three time points could be explained by gender and age. Bonferroni-adjusted pairwise comparison result did not change.

Change in BSI total using repeated measures ANCOVA: The BSI total adjusted by age and gender respectively was not significantly different when all three time points were compared simultaneously: F (2, 46) = 0.285, P = 0.753 and F (2, 46), P = 0.366 (Table 6). As for the covariate higher education, it showed a small increase in the P-value of timepoint from ANOVA results to ANCOVA results: From P = 0.008 (Table 5) to P = 0.071 (Table 6). This suggested part of the difference of BSI total across three time points could be explained by age and gender. Bonferroni-adjusted pairwise comparison result was the same as ANOVA results.

Analysis of BSI items 45 and 46

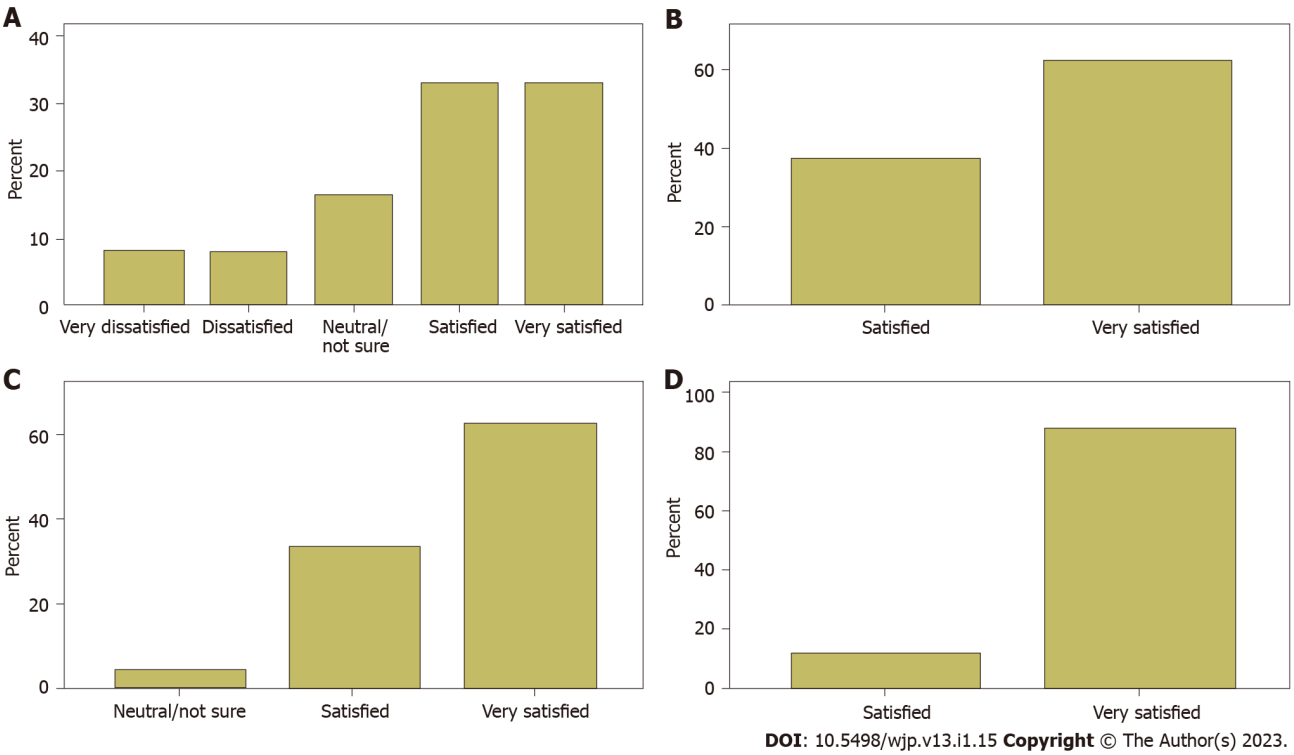
BSI item 45 asked only at baseline 'Have felt that you have been passing urine in the semen?' A total n = 6 men answered "no". BSI item 46 asked at all three time points, 'Have you had difficulty getting a full erection?' All n = 6 male respondents answered "no" at baseline, while post-treatment (n = 4) responded "no" and (n = 1) said "yes", while 1 did not respond. At follow-up timepoint, (n = 4) responded "no" and (n = 2) did not respond.

PEQ post-treatment results

PEQ analysis involved descriptive data on each item relating to the patient experience and satisfaction of the intervention. Figures 7A-D display a graphical presentation of the PEQ items 1, 3, 5, and 10. A total of 24 out of 32 participants completed the questionnaire. There was a significant positive correlation between PEQ item 8 and CORE risk mean (Somers D = 0.5); between PEQ item 8 and HADS Depression (Somers D = 0.67); and between PEQ item 8 and CORE functioning mean (Somers D = 0.69). This meant that the people who had worse scores on risk, functioning, and depression were more engaged with the treatment. However, all other correlations were not significant. Therefore, overall, the experience of treatment was independent of the changes in the outcome scales.

DISCUSSION

Our feasibility study sought to explore how some of the cultural barriers could be addressed with a manual that adapts the CBT based, third-wave based, CCC therapy- for diverse ethnic minority groups. Of the 32 participants within our sample, 3 dropped out before completing a total of 6 sessions. Thus, there is a positive notion for acceptability and adherence to the intervention. Given the ethnic diversity within the study sample, our manual appears to have relevance to operate cross-culturally. Significant improvement on anxiety/depression (HADS, anxiety and depression, BSI, and CORE) and overall quality of life (WHODAS) is suggested within the study sample. Developing the manual in response to challenges posed by the therapy in supervision raised interesting issues that were resolved within the CCC framework. Therefore, the development of CBT approaches built around mindfulness, commonly referred to as the third-wave, promotes a reflective space between the individual's thoughts and feelings, in contrast to the direct challenge, which makes it more acceptable to ethnic minority groups.



DOI: 10.5498/wjp.v13.i1.15 **Copyright** © The Author(s) 2023.

Figure 7 Patient Experience Questionnaire Items. A: How satisfied are you with the amount of time you had to wait for your first appointment? B: How satisfied are you with the type of treatment that you received? C: How satisfied are you with the overall experience of using this service? D: How satisfied are you with the therapist that treated you?

CCC avoids much of the complexity of other therapies by drawing on its roots in cognitive science to target the universal human need to establish a tolerable internal state. Attempts to regain equilibrium where this state is not tolerable led to behaviors and experiences that are then labelled as symptoms.

In addition, difference in cultural attitudes where assertiveness and anger proved amenable to the controlled expression of emotion with a mindfulness approach, which is similar to previous research conducted[18,37]. This could also be an intervention that could aid managing family expectations' to highly sensitive subject matter[6]. Issues that raised religious and cultural sensitivity, such as sexual abuse, required both validation of the individual's experience and acceptance of the limitation of open acknowledgement by the wider group. The relational nature of the interacting cognitive subsystems-based model of the person opens the way to the discussion of religious and faith issues that sidestepped contentious dogmas. CCC enables deep reflection by accommodating cultural adjustments, it makes this process of therapy more applicable and relevant. At present, four studies on CCC have been published looking at acute psychology which is different to the intervention used in this study[43,54-56], while demonstrating the ability of the approach to engage a challenging population. Three more studies are in preparation. Research into CCC is sparse at the moment and this pilot study is preliminary research into the CCC intervention, hence currently lacks any research comparators. The findings of this study are largely in line with previous research on culturally adapted CBT. Previous research found that adaptations in core elements, such as family, therapy delivery, and religious/spiritual views, enabled for the most efficacious outcomes for ethnic minority groups[14,15].

The recognized role of childhood or adult trauma in the development of psychological stress needing clinical management and psychological input is fully incorporated into CCC. The participant characteristics highlight the spectrum of trauma and past adversity contributing to current mental health difficulties across a primary care sample not selected for trauma. In the United Kingdom, National Institute for Health and Care Excellence guidelines provide an important consideration for clinicians who have such patients. Therefore, it is essential that primary, secondary, and tertiary care health professionals are fully aware of such issues to ensure patients receive optimal short, medium, and long-term care that is detrimental to reducing distress and improving their quality of life. Similarly, emotional, and general wellbeing, should be considered as an undercurrent to this intervention that requires to be kept at proximity, when managing ongoing care for these patients. Equally, in the event, potential patients have underlying chronic long-term comorbidities, the correlational aspect should be considered at the time of introducing this intervention and measuring its outcome longitudinally.

The main limitation of this study was that it was an uncontrolled pilot study to assess the feasibility of the manualized intervention. Therefore, the sample size remained sizable to demonstrate an effect size. The sample used was skewed towards female participants (84.4%) and outcome measures were not

adapted accordingly. Future studies should consider gender accountability. The emphasis was on learning from individual therapies with individuals who presented to an IAPT service and a CMHT with a wide range of problems and from diverse ethnicities. In relation to using both primary and secondary care samples, results have shown that both groups accepted in intervention and participant satisfaction was significant. As such, it represents the normal clinical practice in its complexity, making generalization more difficult. However, within these limitations, the results are promising and should merit a more extensive and definitive phase three randomized controlled interventions in the future.

In terms of future research, it would be ideal for a comprehensive randomized study design to be implemented. It would be insightful to include a much larger sample size with proportionate participant numbers from each ethnic group included. This would allow for stronger statistical outputs and more generalizable conclusions regarding the impact of this CaCBT-based third-wave therapy manual.

CONCLUSION

The culturally adapted CBT third-wave based manual intervention showed significant improvement in symptoms (HADS, anxiety and depression and CORE) and overall quality of life (WHODAS) from baseline to post-treatment. The study therapists reported that the adapted CCC formulation was simple, effective, and validated the patients' experiences well. This study adds to the body of knowledge supporting cultural adaptations of evidence-based therapies for diverse and minoritized ethnic groups.

ARTICLE HIGHLIGHTS

Research background

Currently, cognitive behavioral therapy (CBT) is one of the most common interventions implemented to treat symptoms of psychopathology of various illnesses. Standardised CBT manuals may not be completely relevant to all populations for several reasons including cultural and psychosocial variations.

Research motivation

Culturally adapted CBT could be beneficial to individuals of minority ethnic backgrounds as the contextual relevance may elevate the therapeutic benefit. Hence, this paper proposes a CaCBT-based third-wave therapy manual based on the Comprehend, Cope and Connect model.

Research objectives

This study aimed to test the feasibility, acceptability and adherence of the proposed intervention within ethnic minority participants who are currently engaged in Improving Access to Psychological Therapies' iTalk and Community Mental Health Team services that are part of the United Kingdom's National Health Service.

Research methods

In order to test the intervention, an uncontrolled feasibility study was deployed with 32 participants. Various outcome measures were recorded at three time points (baselines, post-intervention, and 12-wk follow-up).

Research results

A repeated measures analysis of variance revealed significant improvements in symptoms across Hospital Anxiety and Depression Scale depression and anxiety scores as well as the Clinical Outcomes in Routine Evaluation total score and World Health Organization Disability Assessment Schedule 2.0 measures.

Research conclusions

The results of this feasibility study reported that the CaCBT-based third-wave therapy was effective. Our results also showed significant adherence and acceptability among minority ethnic participants. Moderate effect sizes were reported with high participant satisfaction levels although a wider clinical trial will be required to fully assess the efficacy and effectiveness of the manual in the future.

Research perspectives

It would be important to further explore a randomised controlled trial as well as its' cost-effectiveness, overall benefit and scalability to a more diverse sample within the United Kingdom. This would aid in conducting wider global clinical trials to better understand the suitability of this adapted intervention.

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FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Identification and characterization of noncoding RNAs-associated competing endogenous RNA networks in major depressive disorder

Zhi-Li Zou, Yu Ye, Bo Zhou, Yuan Zhang

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Abstract

BACKGROUND

Major depressive disorder (MDD) is a common and serious mental illness. Many novel genes in MDD have been characterized by high-throughput methods such as microarrays or sequencing. Recently, noncoding RNAs (ncRNAs) were suggested to be involved in the complicated environmental-genetic regulatory network of MDD occurrence; however, the interplay among RNA species, including protein-coding RNAs and ncRNAs, in MDD remains unclear.

AIM

To investigate the RNA expression datasets downloaded from a public database and construct a network based on differentially expressed long noncoding RNA (lncRNAs), microRNAs (miRNAs), and mRNAs between MDD and controls.

METHODS

Gene expression data were searched in NCBI Gene Expression Omnibus using the search term "major depressive disorder." Six array datasets from humans were related to the search term: GSE19738, GSE32280, GSE38206, GSE52790, GSE76826, and GSE81152. These datasets were processed for initial assessment and subjected to quality control and differential expression analysis. Differentially expressed lncRNAs, miRNAs, and mRNAs were determined, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed, and protein-protein interaction network was generated. The results were analyzed for

their association with MDD.

RESULTS

After analysis, 3 miRNAs, 12 lncRNAs, and 33 mRNAs were identified in the competing endogenous RNA network. Two of these miRNAs were earlier shown to be involved in psychiatric disorders, and differentially expressed mRNAs were found to be highly enriched in pathways related to neurogenesis and neuroplasticity as per Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses. The expression of hub gene fatty acid 2-hydroxylase was enriched, and the encoded protein was found to be involved in myelin formation, indicating that neurological development and signal transduction are involved in MDD pathogenesis.

CONCLUSION

The present study presents candidate ncRNAs involved in the neurogenesis and neuroplasticity pathways related to MDD.

Key Words: Major depressive disorder; Noncoding RNA; Competing endogenous RNA; Bioinformatics; Data mining

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Core Tip: Competing endogenous RNAs (ceRNAs) are novel regulatory molecules involved in a wide range of biological processes and diseases. This study explored the potential ceRNA networks (ceRNETs) involved in the pathogenesis of major depressive disorder (MDD) using bioinformatics data mining. A ceRNET comprising 3 miRNAs, 12 lncRNAs, and 33 mRNAs was constructed based on two public datasets obtained from the Gene Expression Omnibus database. Elucidating the correlation of the ceRNET with MDD opens new avenues to discover specific diagnostic biomarkers for MDD and expands our knowledge about this disease.

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INTRODUCTION

Major depressive disorder (MDD), characterized by persistent and intense feelings of sadness for extended periods, is one of the most common causes of morbidity and mortality worldwide[1], yearly affecting approximately 5% of adults worldwide[2]. The exact cause of MDD remains unknown; however, the occurrence of MDD is widely believed to involve crosstalk between genetic, environmental, social, and developmental vulnerabilities and resilience factors[2,3]. Numerous risk factors for MDD have been identified from three major perspectives: medical, social, and substance[4,5]. Available treatment options primarily include pharmacotherapy, psychotherapy, and lifestyle changes. However, prevention and treatment of this disease remain difficult because of varying presentations, unpredictable course and prognosis, and variable responses to treatment[6]. Therefore, further studies are needed to determine the biological mechanisms underlying MDD to develop better patient therapies.

The increasing popularity of high-throughput microarray technologies has facilitated the identification of genome variations in MDD, improving the understanding of its pathogenesis and development, and revealing promising biomarkers. Gao *et al*[7] identified 241 differentially expressed genes (DEGs) in the hippocampus (hip), 218 DEGs in the prefrontal cortex (pfc), and 327 DEGs in the striatum (str) from patients with MDD. These DEGs were enriched in glycan biosynthesis, RIG-I-like receptor signaling, and pyrimidine metabolism pathways, which significantly contribute to MDD pathogenesis. Additionally, the DEGs AR, PTK2, IRAK1, IL12A, GALNT12, GALNT2, CD19, and PTDSS2 were identified as novel therapeutic targets[7,8]. Moreover, Segman *et al*[9] found 73 DEGs between patients with postpartum major depression and controls using peripheral blood cells; the immune response, transcriptional effects on cell proliferation, and DNA replication and repair were significantly enriched in these patients. Although novel genes have been discovered and well-studied, genetic predisposition to MDD only partly explains the occurrence of this illness. With the development of epigenetic theory and technology, non-coding RNAs (ncRNAs) have been identified to help explain the interaction between genetics and the environment. Li *et al*[10] found an inverse relationship between serum brain-derived neurotrophic factor (BDNF) levels and miR-132/miR-182 levels in depression, supporting the

notion that miR-182 is a putative regulatory microRNA (miRNA) of BDNF. Zhou *et al*[11] found that miRNAs act as key regulators of synaptic plasticity in MDD pathogenesis. Liu *et al*[12] detected four long non-coding ribonucleic acids (lncRNAs) related to the expression of mRNAs associated with MDD. Although ncRNAs have been proposed to play important roles in MDD, the regulatory network among RNA species remains unclear.

The competing endogenous RNA (ceRNA) network proposed by Salmena *et al*[13] has been verified in an increasing number of studies. This complicated post-transcriptional regulatory network plays a critical role in the progression and pathogenesis of various illnesses, including cancer. However, to date, no ceRNA network has been proposed for MDD. Here, we investigated RNA expression datasets downloaded from the Gene Expression Omnibus (GEO) database and constructed a network based on differentially expressed lncRNAs, miRNAs, and mRNAs between MDD and controls. This network was used to mine for functional ncRNAs that may contribute to the epigenetic mechanism underlying MDD pathogenesis and may be useful as potential therapeutic targets and biomarkers for MDD.

MATERIALS AND METHODS

Data resources and preprocessing

Gene expression data were searched in NCBI GEO using the search term "major depressive disorder". Six array datasets from humans were related to the search term: GSE19738 (expression profiling by array, n = 42; MDD, 21; control, 21), GSE32280 (expression profiling by array, n = 24; MDD, 8; subsyndromal symptomatic depression, SSD, 8; control, 8), GSE38206 (expression profiling by array, n = 18; MDD, 9; control, 9), GSE52790 (expression profiling by array and ncRNA profiling by array, n = 22; MDD, 10; control, 12), GSE76826 (expression profiling by array, n = 22; MDD, 10; control, 12), and GSE81152 (ncRNA profiling by array, n = 50; MDD, 31; control, 19). These datasets were processed for initial assessment; if they met the requirements, they were subjected to quality control and differential expression analysis.

Identification of differentially expressed lncRNAs, miRNAs, and mRNAs

The differentially expressed mRNAs, lncRNAs, or miRNAs were determined based on the threshold criteria of $|\log2 \text{(fold-change)}| \geq 1$ and an adjusted P value < 0.05 using the R limma package (version 3.40.6). The differentially expressed lncRNAs (DE_lncRNAs) obtained from GSE76826 were entered into the miRcode database (http://www.mircode.org/) that provides an integrated, searchable map of putative target sites of miRNAs, to predict the interactions of DE_lncRNAs and DE_miRNAs. Only DE_lncRNAs for which miRNAs were successfully predicted were selected for ceRNA network construction. The miRNAs obtained were overlapped with differentially expressed miRNAs obtained from GSE81152, and the overlapping miRNAs were identified as a differentially expressed miRNA (DE_miRNA). The name of the DE_miRNA was entered into the miRDB (http://mirdb.org/) and TargetScan (http://www.targetscan.org/vert_72/) databases, both of which are online databases used to predict miRNA targets. The mRNAs obtained above were overlapped with differentially expressed RNAs identified from GSE76826. The DE_lncRNAs, DE_miRNAs, and DE_mRNAs obtained in the manner described above were used for ceRNA network construction.

DE_lncRNA/DE_miRNA/DE_mRNA network construction

Cytoscape 3.4.0 was used to visualize the DE_lncRNA/DE_miRNA/DE_mRNA network construction.

Gene Ontology function and Kyoto Encyclopedia of Genes and Genome pathway enrichment analysis

To help identify the potential biological functions of these genes in the MDD ceRNA network, Gene Ontology (GO) functional and Kyoto Encyclopedia of Genes and Genome (KEGG) pathway enrichment analyses were performed using the clusterProfiler package in R. GO terms have three categories; biological process, cellular compartment, and molecular function. $P \leq 0.05$ indicated a significant difference in GO terms and KEGG pathways.

Construction of the protein interaction network

The protein interaction (PPI) network was constructed to evaluate the interactions among genes. The DE_mRNAs were selected to construct a PPI network based on Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) ver.11.0 (https://string-db.org/). In the PPI network, a node represents a gene; the undirected link between two nodes is an edge, representing the interaction between two genes, and the degree of a node corresponds to the number of interactions of a gene with other genes in the network.

RESULTS

Quality control and differential expression analysis

The workflow of the analysis is shown in Figure 1. Because the GSE19738 dataset lacks documents to annotate gene symbols and the GSE32280 dataset uses peripheral blood mononuclear cells rather than whole blood, both these datasets were excluded from analysis at the first stage. Next, sample-level quality control was performed using principal component analysis to ensure that the cases and controls were well-separated and to identify sample outliers. After removing the outliers, there were 10 controls and 8 MDD cases in GSE52790, 12 controls and 9 MDD cases in GSE76826, and 10 controls and 23 MDD cases in GSE81152. The four remaining datasets, GSE32280, GSE52790, GSE76826, and GSE81152, were utilized to identify differentially expressed mRNAs, lncRNAs, and miRNAs using the limma R package with the threshold set to an adjusted P value < 0.05 and $|\log2 \text{(fold-change)}| \geq 1$. A hierarchical cluster heatmap showing the expression patterns of the DEGs between MDD and controls is shown in Figure 2. As no DEGs were found in GSE32280, this dataset was excluded from subsequent analysis. A total of 125, 373, and 54 DEGs were identified in the GSE52790, GSE76826, and GSE81152 datasets, respectively. There were 112 upregulated and 13 downregulated genes among the 125 DEGs in GSE52790, 109 upregulated genes (including 89 mRNAs and 10 lncRNAs) and 264 downregulated genes (including 198 mRNAs and 66 LncRNAs) in the 373 DEGs of GSE76826, and 51 upregulated and 3 downregulated genes in the 54 DEGs of GSE81152.

Construction of a ceRNA network for MDD

To better understand the effect of lncRNAs on mRNAs mediated by combinations with miRNAs in MDD, we constructed a ceRNA network based on the GSE76826 and GSE81152 data. Eighty-six differentially expressed lncRNAs from GSE76826 were retrieved and entered into the miRcode database to predict the potential interacting miRNAs. Eighty-four miRNAs (645 LncRNA-miRNA pairs) were identified in the miRcode database. Next, we overlapped these 84 miRNAs to the differentially expressed miRNAs identified in GSE81152, generating 3 shared miRNAs (the corresponding lncRNAs were reduced to 12) (Table 1). Thereafter, we entered these 3 miRNAs into the miRDB and TargetScan databases to identify their potential target mRNAs and combined the results from these two databases to achieve high true-positive coverage. A total of 1,868 mRNAs was generated from the two databases; when the 287 differentially expressed mRNAs identified from GSE76826 were overlapped, 33 shared mRNAs were identified (Table 2). Finally, we assembled all identified ceRNA pairs to generate an mRNA-miRNA-lncRNA network in MDD (Figure 3).

Gene set enrichment analysis

Enrichment analysis indicated that the 33 differentially expressed mRNAs were significantly associated with the GO terms for 887 biological process, 105 molecular function, and 55 cell component terms. For the KEGG pathways, the only significant pathway was the mammalian target of rapamycin (mTOR) signaling pathway. Table 3 and Figure 4 list the top 10 most significant biological processes, molecular functions, and cellular components from the GO terms.

PPI network construction

A total of 33 DEG mRNAs were entered into the STRING database to build a PPI network. Gene nodes with the highest W values in the network were *ACVR1C*, *ELOVL4*, *fatty acid 2-hydroxylase* (*FA2H*), *INHBB*, *NIPAL4*, and *UGT8* (Figure 5).

DISCUSSION

Considerable progress has been made in understanding the pathophysiology of MDD; however, no single model or mechanism can fully explain all aspects of the disease[6]. MDD is believed to involve the following: Reduced levels of monoamines, changes in the hypothalamic-pituitary-adrenal axis, inflammation, limited neurogenesis, changes in brain structure and function, heredity factors, environmental milieu, and epigenetics[6]. Epigenetics, a field focusing on gene-environment interactions, has gained attention over the past decades. The recent application of microarray-based genome-wide expression analysis has enabled the identification of MDD-associated genes, including novel ncRNAs. Although numerous studies have demonstrated that ncRNAs play important roles in MDD pathogenesis, the mechanisms of how these genes regulate MDD have not been well-characterized[14, 15]. Thus, we performed ceRNA network analysis by data mining to determine the potential regulatory mechanisms of MDD.

Multiple GO terms were identified in enrichment analysis, reflecting the complexity of the disorder. We observed that protein-coding genes in the network were highly correlated with cellular growth and developmental differentiation, including the activin receptor signaling pathway, peripheral nervous system development, G protein-coupled receptor internalization, receptor-ligand activity, hormone

Table 1 The twenty differentially expressed long noncoding RNAs and differentially expressed_microRNA pairs identified in this study

lncRNA	miRNA
STAG3L4	hsa-miR-4465
MTERFD2	hsa-miR-4465
TCL6	hsa-miR-4465
MDS2	hsa-miR-4465
LINC00202	hsa-miR-4465
LINC00402	hsa-miR-4465
TCL6	hsa-miR-137
ANKRD36BP2	hsa-miR-137
LINC00202	hsa-miR-137
LINC00402	hsa-miR-137
MIR600HG	hsa-miR-137
MTERFD2	hsa-miR-125b-5p
HCG4	hsa-miR-125b-5p
TCL6	hsa-miR-125b-5p
UBE2Q2P2	hsa-miR-125b-5p
TREML2P1	hsa-miR-125b-5p
KIAA0125	hsa-miR-125b-5p
ANKRD36BP2	hsa-miR-125b-5p
LINC00202	hsa-miR-125b-5p
MIR600HG	hsa-miR-125b-5p

lncRNA: Long noncoding RNA; miRNA: microRNA.

activity, growth factor activity, and cellular growth. The term "signaling by activins" in our results is consistent with previous studies showing that activin can modulate depression and anxiety-related behavior[16-21]. Activins are members of the transforming growth factor-β superfamily that are expressed in various tissues, including neuronal cells, and are involved in proliferation, differentiation, metabolism, homeostasis, apoptosis, immune response, and tissue repair. Postnatal neurogenesis, which leads to the production of new neurons in the adult brain, can influence the replacement of damaged neurons, stress responses, memory formation, and depression, among others[22]. Previous studies have reported that the activin activity in the adult forebrain influences locomotor activity, anxiety-related behavior, and hippocampal neurogenesis, which is also associated with age-related cognitive decline [23]. Additionally, consistent with our results, utilizing a genome-wide association study, Smeeth *et al* [23] suggested a complex relationship among reproductive hormones, hippocampal neurogenesis, and depression. Based on transcriptome array results analysis of Chinese patients with MDD, Liu *et al*[12] reported the enrichment of differentially expressed coding genes in the signal transduction pathway and basic metabolic process associated with neurodevelopmental disease[12,13]. Our KEGG results also showed that the mTOR signaling pathway is a part of the regulatory network of MDD. This agrees with previous studies which showed that the mTOR signaling pathway, which senses and integrates diverse extracellular stimuli to promote cellular growth or limit catabolic processes, contributes to normal neuronal growth and is associated with neurogenesis[24]. Notably, the mTOR signaling pathway has become an important target for treating depression using drugs such as ketamine[25,26].

The use of ncRNAs as biomarkers of psychological disorders is gaining momentum. In the ceRNA network developed in this study, there were 12 lncRNAs, 3 miRNAs, and 33 mRNAs specific to MDD. Consistent with our results, hsa-mir-137, as a brain-enriched miRNA, was earlier confirmed as a gene related to MDD, bipolar disorder, schizophrenia, and Parkinson's disease susceptibility[27-30], whose underlying mechanisms regulate synaptic plasticity. Moreover, Zhao *et al*[31] detected significantly lower hsa-miR-137 Levels in the brain and peripheral blood in post-stroke depression rats, and Kim *et al* [32] found that it can be used as a diagnostic marker for methamphetamine withdrawal syndrome. Similarly, hsa-miR-125b-5p in the peripheral blood is highly expressed in Alzheimer's disease compared with that in controls.

Table 2 The forty-three differentially expressed_mRNAs and differentially expressed microRNA pairs identified in this study

miRNA	mRNA
hsa-miR-4465	FAM98B
hsa-miR-4465	ADM
hsa-miR-4465	INHBB
hsa-miR-4465	FA2H
hsa-miR-4465	HOXA9
hsa-miR-4465	GRB10
hsa-miR-4465	UGT8
hsa-miR-4465	ACVR1C
hsa-miR-4465	COL19A1
hsa-miR-4465	TTC28
hsa-miR-4465	HAS3
hsa-miR-4465	SLC22A23
hsa-miR-4465	ADAM23
hsa-miR-4465	NACC2
hsa-miR-4465	SH3PXD2A
hsa-miR-4465	CELSR1
hsa-miR-4465	PLEKHG1
hsa-miR-4465	ZSWIM5
hsa-miR-137	AKAP2
hsa-miR-137	HLF
hsa-miR-137	FGF9
hsa-miR-137	GLIS2
hsa-miR-137	SIPA1L2
hsa-miR-137	WNT7A
hsa-miR-137	NRG1
hsa-miR-137	ADAM23
hsa-miR-137	LRRC4
hsa-miR-137	SLC22A23
hsa-miR-137	COL19A1
hsa-miR-137	TTC28
hsa-miR-137	APLN
hsa-miR-137	NACC2
hsa-miR-137	BACH2
hsa-miR-137	ACVR1C
hsa-miR-125b-5p	NIPAL4
hsa-miR-125b-5p	NR6A1
hsa-miR-125b-5p	ZSWIM5
hsa-miR-125b-5p	GALNT14
hsa-miR-125b-5p	GRB10
hsa-miR-125b-5p	ELOVL4
hsa-miR-125b-5p	ACVR1C

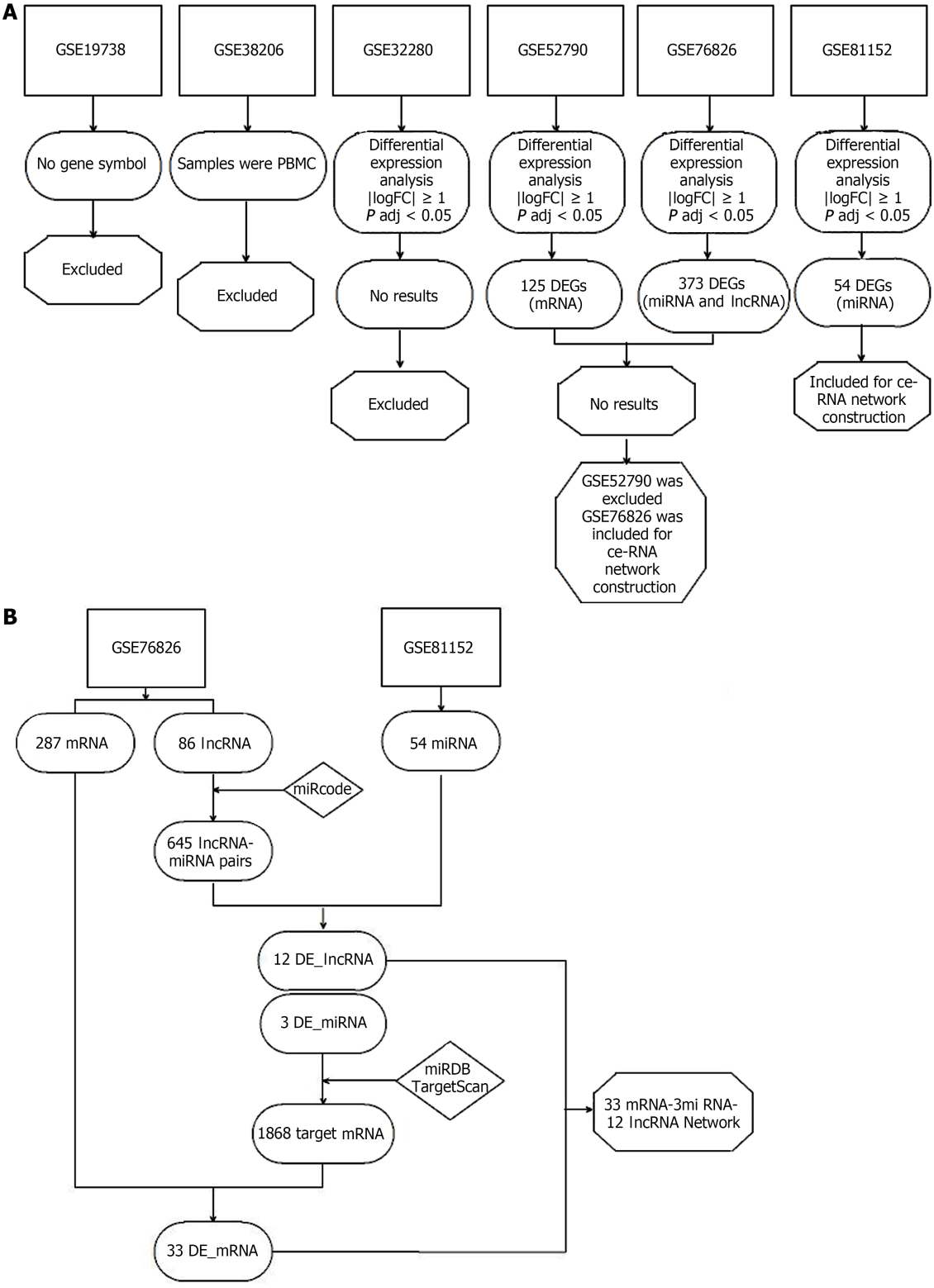
hsa-miR-125b-5p	RALGPS2
hsa-miR-125b-5p	GLIS2

FA2H: Fatty acid 2-hydroxylase.

Table 3 The significant Gene Ontology terms identified in this study

Category	Term description	Count of genes	*P* value
Biology process	Activin receptor signaling pathway	3	5.54E-05
Biology process	Peripheral nervous system development	3	0.000292
Biology process	G protein-coupled receptor internalization	2	0.0003
Biology process	Desensitization of G protein-coupled receptor signaling pathway	2	0.000487
Biology process	Negative adaptation of signaling pathway	2	0.000487
Biology process	Positive regulation of vascular endothelial growth factor receptor signaling pathway	2	0.000487
Biology process	Adaptation of signaling pathway	2	0.000597
Biology process	Uterus development	2	0.000656
Biology process	Sphingolipid biosynthetic process	3	0.000679
Biology process	Reproductive structure development	5	0.00078
Cellular component	Glutamatergic synapse	4	0.002395
Cellular component	Schaffer collateral-CA1 synapse	2	0.00786
Cellular component	Cul2-RING ubiquitin ligase complex	1	0.024149
Cellular component	Integral component of synaptic membrane	2	0.025933
Cellular component	Intrinsic component of synaptic membrane	2	0.029786
Cellular component	Extracellular matrix	3	0.044750
Cellular component	Podosome	1	0.047732
Cellular component	Excitatory synapse	1	0.075303
Cellular component	Integral component of postsynaptic density membrane	1	0.079823
Cellular component	Intrinsic component of postsynaptic density membrane	1	0.084321
Molecular function	Receptor ligand activity	6	0.000191
Molecular function	Hormone activity	3	0.001352
Molecular function	UDP-glycosyltransferase activity	3	0.002314
Molecular function	Guanyl-nucleotide exchange factor activity	4	0.002772
Molecular function	Growth factor activity	3	0.003326
Molecular function	Transferase activity, transferring hexosyl groups	3	0.006074
Molecular function	Phosphatidylinositol-4,5-bisphosphate 3-kinase activity	2	0.006746
Molecular function	Cytokine activity	3	0.007189
Molecular function	Phosphatidylinositol bisphosphate kinase activity	2	0.007334
Molecular function	Transcription factor activity, RNA polymerase II proximal promoter sequence-specific DNA binding	4	0.008356

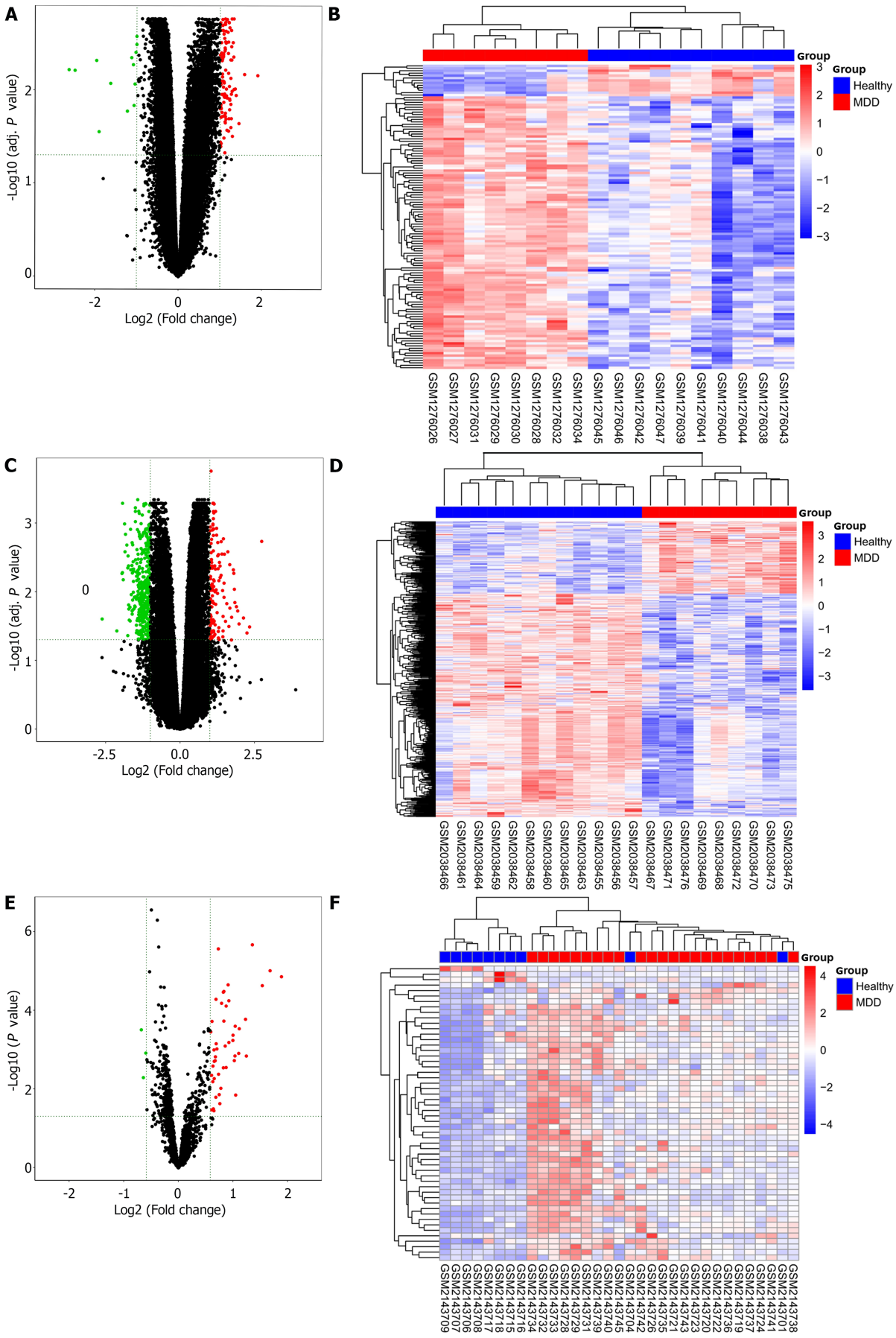
In addition to genetic components, different epigenetic mechanisms play an important role in the occurrence and development of MDD. A previous study revealed that the non-protein-coding RNA repressor of NFAT, human accelerated region 1, transcribed antisense of rheelin, and B-secretase-1 are associated with cognitive function, potentially contributing to MDD, and the lncRNA BDNF-AS was reportedly related to synaptic plasticity and potentially associated with MDD[33-36]. In a recent study, Abedpoor and colleagues reported that the lncRNA network could play an indispensable role in regulating depression-like behaviors in mice[37]. Furthermore, two studies reported lower RMRP expression in a mouse model of depression and MDD relative to normal subject samples[14]. In another



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Figure 1 Flowchart of the study. A: Step 1, dataset screening; B: Step 2, competing endogenous RNA network construction. DEGs: Differentially Expressed Genes; mRNA: Messenger RNA; miRNA: MicroRNA; lncRNA: Long non-coding RNA; ceRNA: Competing endogenous RNAs; miRcode: http://www.mircode.org/; miRDB: http://mirdb.org/; TargetScan: http://www.targetscan.org/vert_72/; DE_mRNA: Differentially expressed mRNA; DE_lncRNA: Differentially expressed lncRNA; DE_miRNA: Differentially expressed miRNA.

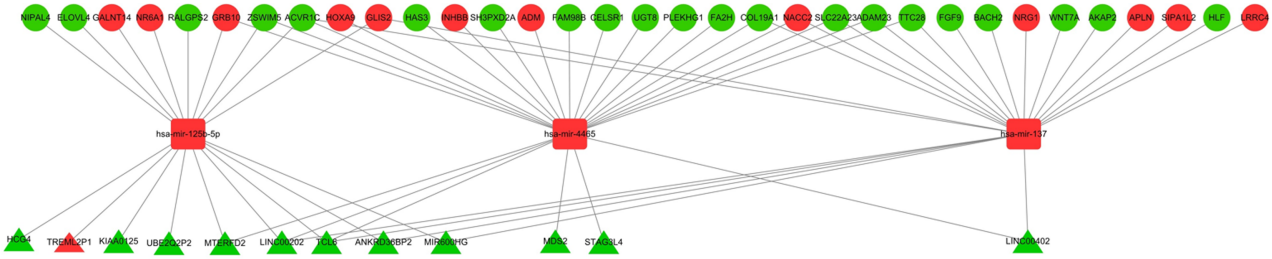
study, Issler *et al*[38] observed that LINC00473 was downregulated in the prefrontal cortex of depressed females. Collectively, these results suggest that lncRNAs are potential diagnostic and prognostic biomarkers. Our results revealed 12 different lncRNAs involved in the MDD ceRNA network, suggesting the existence of a regulatory network in MDD.



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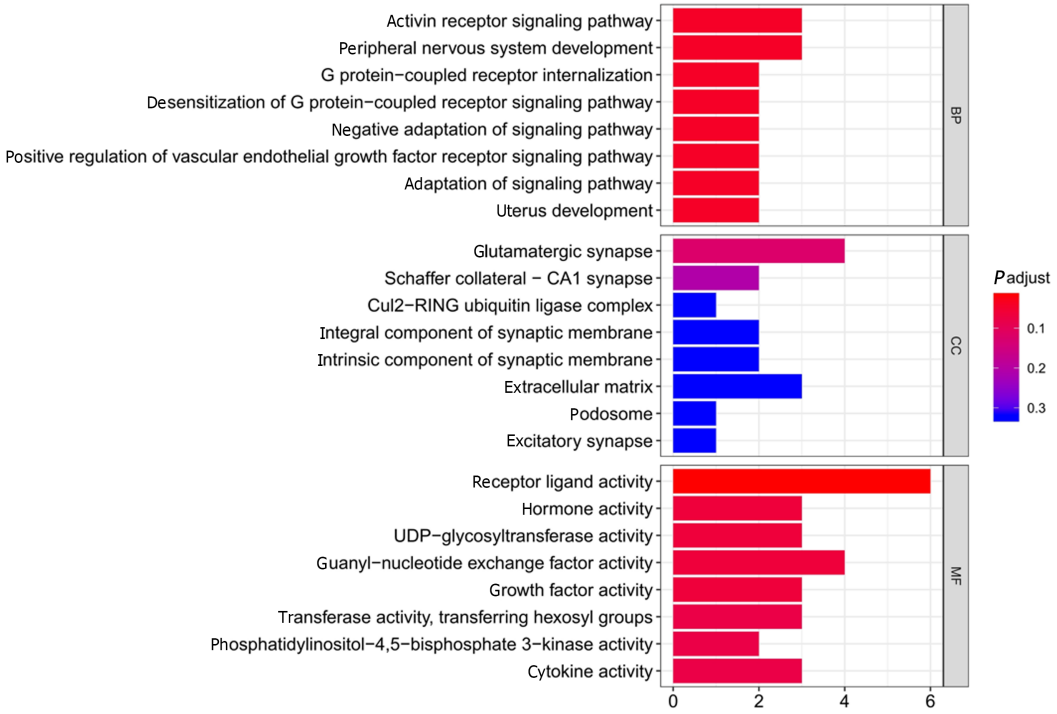
Figure 2 Difference and cluster analyses. A: Volcanic maps of differentially expressed genes in GSE52790; B: Cluster analysis heatmap of the expression patterns of the differentially expressed genes in GSE52790; C: Volcanic maps of differentially expressed genes in GSE76826; D: Cluster analysis heatmap of the

expression patterns of the differentially expressed genes in GSE76826; E: Volcanic maps of differentially expressed genes in GSE81152; F: Cluster analysis heatmap of the expression patterns of the differentially expressed genes in GSE81152. Red indicates upregulated genes; green indicates downregulated genes.



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Figure 3 Major depressive disorder-associated enriched competing endogenous RNA network. Red and green indicate upregulated downregulated genes, respectively. The circles represent differentially expressed RNA (DE_RNA), triangles represent DE long noncoding RNA (DE_lncRNA), and rounded squares represent DE_microRNA.

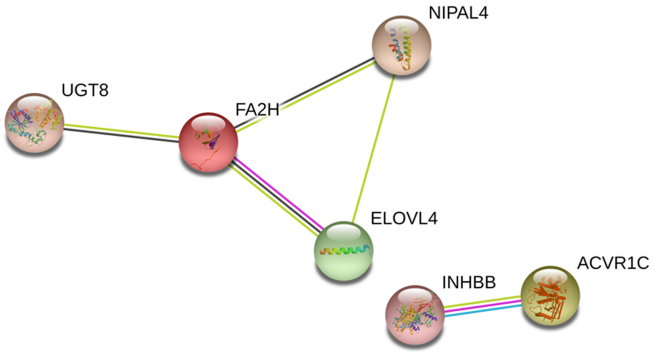


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Figure 4 Gene Ontology functional enrichment analysis.

In the present study, FA2H was highlighted in the PPI network. FA2H encoded by *FA2H* is highly expressed in the human brain and is involved in the formation of 2-hydroxy galactosylceramides and 2-hydroxy sulfatides in myelin[39,40]. The FA2H gene appears to be related to lipid metabolism and is one of the 10 candidate genes identified in an inherited neurologic disorder known as neurodegeneration with brain iron accumulation and is also involved in hereditary spastic paraplegia SPG35 and leukodystrophy[41,42]. Mutations in FA2H have been identified in autism spectrum disorders[43]. The function of FA2H does not appear to be limited to the brain since elevated FA2H expression has also been found in hepatocellular carcinoma and lung adenocarcinoma involving UGT8[44,45]. However, there have been no reports of FA2H in MDD and thus, this is the first study to suggest that FA2H is related to MDD. Considering its role in myelin formation, this gene may contribute to MDD pathogenesis *via* impacting neurological development and modulating signal transduction.

Elongation of very long-chain fatty acids-4 (ELOVL4) was another protein of interest identified in the PPI. This protein is essential for the synthesis of very long-chain polyunsaturated (VLC-PUFA) and saturated fatty acids (VLC-SFA) of chain lengths greater than 26 carbons[46]. The VLC-PUFAs play an important role in maintaining neural tissue homeostasis. Studies have suggested that dysregulated



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Figure 5 Protein interaction network construction. FA2H: Fatty acid 2-hydroxylase.

ELOVL4 expression may be involved in the lipid alterations observed in neuroblastoma, and mutations in the ELOVL4 gene could cause several distinct neurodegenerative diseases, including stargardt-like macular dystrophy, spinocerebellar ataxia 34, and a neuro-ichthyotic syndrome with severe seizures and spasticity[47,48]. However, like FA2H, none of the studies so far have linked ELOVL4 and MDD, and therefore, future validation benchmark experiments are needed.

There were some limitations to our study. The potentially important genes associated with MDD lack gene expression and functional validation, and hence, further *in vivo* and *in vitro* studies are required. Furthermore, the two datasets were not from the same platform, which may have resulted in a few deviations. However, the present study provides novel insight into MDD pathogenesis.

CONCLUSION

To date, MDD diagnosis mainly depends on the patient's subjective expression, which may be misinterpreted by clinicians. Therefore, identification of a reliable biomarker that can be used to diagnose MDD and guide its treatment is imperative. In conclusion, the present study revealed that hsa-miR-4465, hsa-miR-137, and hsa-miR-125b-5p may be useful genetic biomarkers for MDD as they are potentially involved in the neurogenesis and neuroplasticity pathways in MDD. These results require further validation in future studies.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) is a common and serious mental illness. Many novel genes in MDD have been characterized by high-throughput methods such as microarrays or sequencing. Recently, noncoding RNAs (ncRNAs) were suggested to be involved in the complicated environmental-genetic regulatory network of MDD occurrence.

Research motivation

The interplay among RNA species, including protein-coding RNAs and ncRNAs, in MDD remains unclear.

Research objectives

To investigate the RNA expression datasets and construct a network based on differentially expressed long noncoding RNA (lncRNAs), miRNAs, and mRNAs between MDD and controls through data mining method.

Research methods

Gene expression data were searched and downloaded from NCBI Gene Expression Omnibus database. Six array datasets from humans were related to the search term: GSE19738, GSE32280, GSE38206, GSE52790, GSE76826, and GSE81152. These datasets were processed for initial assessment and subjected to quality control and differential expression analysis. Differentially expressed lncRNAs, miRNAs, and mRNAs were determined, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were performed, and protein-protein interaction network was generated. The results were analyzed for their association with MDD.

Research results

After analysis, 3 miRNAs, 12 lncRNAs, and 33 mRNAs were identified in the ceRNA network. Two of these miRNAs were earlier shown to be involved in psychiatric disorders, and differentially expressed mRNAs were found to be highly enriched in pathways related to neurogenesis and neuroplasticity as per Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses. The expression of hub gene fatty acid 2-hydroxylase was enriched, and the encoded protein was found to be involved in myelin formation, indicating that neurological development and signal transduction are involved in MDD pathogenesis.

Research conclusions

The present study presents candidate ncRNAs involved in the neurogenesis and neuroplasticity pathways related to MDD.

Research perspectives

Bioinformatic data mining method can be an cost-effective way to explore potential biomarkers for complicated diseases. However, benchmark experiment is needed in the future to validate the results.

FOOTNOTES

Author contributions: Zou ZL contributed to study design, manuscript preparation, inspection, and revision; Ye Y contributed to manuscript preparation; Bo Z contributed to study design; Zhang Y contributed to study design and manuscript preparation.

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ORIGINAL ARTICLE

Retrospective Study

Relationship between family cohesion/adaptability and postpartum depressive symptoms: A single-center retrospective study

Guo-Rong Zhang, Peng-Sheng Li, Yan-Bin Jia

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Abstract

BACKGROUND

Depression is the most common mental illness in postpartum mothers, and the etiology of postpartum depression remains poorly understood. Over the past several decades, studies have reported that postpartum depression is caused by multiple factors, such as genetic, psychological, pregnancy, and environmental factors, with the family environment being an important environmental factor. The theory of family cohesion and adaptability put forward by Olson is a classic model that describes the level of family function. However, to date, this model has not been examined regarding its applicability to patients with postpartum depression.

AIM

To investigate the relationship between family cohesion and adaptability and the risk of postpartum depressive symptoms.

METHODS

We retrospectively analyzed 1446 patients admitted to the postpartum healthcare clinic of the Affiliated Foshan Maternity and Child Healthcare Hospital from April 2021 to December 2021. Patients were grouped according to whether postpartum depression symptoms were reported (symptoms, n = 454; no symptoms, n = 992). All patients completed the Edinburgh Postpartum Depression Scale and the Chinese version of the Family Cohesion and Adaptability Assessment Scale II. Baseline and clinical data were compared between groups. Univariate regression analysis was used to investigate the association between different types of family cohesion and postpartum depressive symptoms and the association between different family adaptability types and postpartum

depressive symptoms.

RESULTS

After adjusting for age, education, occupation, gravidity, parity, and mode of delivery, disengaged [adjusted odds ratio (AOR) = 3.36, 95%CI: 1.91–5.91], and separated (AOR = 1.97, 95%CI: 1.34–2.90) family cohesion types showed a higher risk of postpartum depression than the connection type, whereas the enmeshed type (AOR = 0.38, 95%CI: 0.28–0.51) protected against postpartum depressive symptoms. Rigid (AOR = 4.41, 95%CI: 3.02–6.43) and structured families (AOR = 1.88, 95%CI: 1.34–2.63) had a higher risk of postpartum depressive symptoms than flexible families, whereas chaotic families (AOR = 0.35, 95%CI: 0.24–0.51) protected against postpartum depressive symptoms.

CONCLUSION

Family cohesion and adaptability are influencing factors for postpartum depressive symptoms, with higher family cohesion and adaptability being associated with a lower risk of postpartum depressive symptoms.

Key Words: Family cohesion; Adaptability; Postpartum depressive symptoms; Cross-sectional study

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Core Tip: Postpartum depression is the most common mental illness in postpartum mothers; studies have reported that postpartum depression is caused by multiple factors. This study analyzed the family environments of 1446 postnatal women, showing that high family cohesion and adaptability prevented the development of postpartum depressive symptoms. Further, we observed a linear relationship between family cohesion, adaptability, and postpartum depressive symptoms, where higher family cohesion and adaptability scores were associated with a risk of postpartum depressive symptoms.

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INTRODUCTION

Postpartum depression is the most common mental illness in postpartum mothers. In high-income countries, more than 10% of postpartum women experience postpartum depression, and the prevalence is higher in low-income countries[1,2]. Postpartum depression is a leading cause of death for postpartum women, and numerous studies have suggested that postpartum depression in mothers affects the developmental processes of their children, including cognitive and language delays, behavioral problems, unsafe attachment, decreased academic performance, and increased risk of depression in adulthood[3,4]. Postpartum depression places heavy burdens on families and society. Therefore, early detection and intervention of postpartum depressive symptoms are crucial for prevention and treatment.

The etiology of postpartum depression remains poorly understood. Over the past several decades, studies have reported that postpartum depression is caused by multiple factors, such as genetic, psychological[5], pregnancy[6], and environmental factors[7-10]. Guan *et al*[11] found that a poor family environment contributes to the development of postpartum depression, and family communication, emotional responses, and other related factors influence the development of postpartum depression. A study conducted in Japan found that women who live with family members who have a high level of perception and participate in parenting have a low risk of postpartum depression[12]. In addition, Kızılırmak reported a significant negative correlation between Edinburgh Postnatal Depression Scale (EPDS) scores and the total scores for spousal, emotional, social, and physical support in postpartum women[13]. In terms of marital satisfaction, pregnant women who are unsatisfied with the quality of their marriage are more likely to suffer from postpartum depression[14]. A large retrospective study on the correlation between postpartum depression and domestic violence among Asian mothers found that women who experience domestic violence from their partners are at high risk of developing postpartum depression. Moreover, violence and intimidation by other family members are associated with the incidence of postpartum depression, and domestic violence increases the risk of suicidal ideation in patients with postpartum depression[15].

The theory of family cohesion and adaptability put forward by Olson is a classic model that describes the level of family function[16,17]. Family cohesion reflects the robustness of family members' emotional ties and refers to the ability of family members to support each other, unite, and overcome difficulties when dealing with family difficulties. Family adaptability reflects the flexibility of families to deal with changes and is based on the ability to change family power structures or roles in the process of family development. However, to date, this model has not been examined regarding families of patients with postpartum depression. In this study, we conducted a cross-sectional survey among postpartum women in China to explore the effects of family cohesion and adaptability on postpartum depressive symptoms and provide a reference for treatment.

MATERIALS AND METHODS

Participants

We retrospectively analyzed 1446 patients admitted to the postpartum healthcare clinic of the Affiliated Foshan Maternity and Child Healthcare Hospital from April 2021 to December 2021. According to whether postpartum depression symptoms were reported, patients were divided into a postpartum depression symptoms group and a no postpartum depression symptoms group. The inclusion criteria were: (1) Postpartum women of Han ethnicity (self-reported) in China aged 18–45 years; (2) no cognitive, intellectual, or behavior disorders; (3) voluntary participation in the study and ability to independently complete the questionnaires; (4) no serious complications during pregnancy and childbirth and no postpartum child death; and (5) an Apgar score of 8–10. The exclusion criteria were: (1) Postpartum women with major traumatic stress events in the last month, such as spouse death, divorce, and domestic violence; (2) severe or unstable somatic disease; and (3) previous diagnosis of schizophrenia, depression (including postpartum depression), bipolar disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic attacks, or epilepsy.

Postpartum depressive symptoms

The EPDS was used to measure postpartum depressive symptoms. The EPDS was developed in 1987 and is used specifically for screening for postpartum depression. The scale has good reliability and validity. The total score of the scale ranges from 0 to 30, where a higher score indicates greater severity of depression. The Chinese version of the EPDS has been shown to have good reliability and validity [18]. In the Chinese version, the demarcation of depressive symptoms is divided into nine points.

Family adaptability and cohesion

Family cohesion and adaptability were measured using the Family Cohesion and Adaptability Scale (FACES II-CV). FACES II-CV was developed by Olson in 1982 and translated into Chinese by Fei *et al* [19]. The scale evaluates the cohesion and adaptability of families across a total of 30 items, which are scored on a 5-point Likert scale. A higher score indicates better family cohesion and adaptability. Family cohesion is divided into four types based on the total subscale score: disengaged (< 55.9), separated (55.9–63.9), connected (63.9–71.9), and enmeshed (> 71.9). Family adaptability is divided into four types: rigid (< 44.7), structured (44.7–50.9), flexible (50.9–57.1), and chaotic (> 57.1). We only used the section on actual family status, and Cronbach's alpha for this section was 0.93.

Covariates

Age[20], occupation[20], education[21], mode of delivery[22,23], gravidity, and parity[24] have previously been reported to be associated with postpartum depressive symptoms. Therefore, we included them as covariates in this study. The occupation was divided into "unit head", "professional and technical personnel", "clerks", "business and service personnel", "unemployed/housewife", and "other". Educational level was defined by participants' highest level of education, and responses included "junior high school or below", "senior high school", and "college or university". The mode of delivery was divided into "vaginal delivery" and "cesarean section".

Statistical analysis

The cohesion and adaptability of women with and without postpartum depressive symptoms are represented as mean ± SD and were compared using the Student's *t*-test. Age, occupation, educational level, mode of delivery, gravidity, and parity are described using frequency and rate and were compared using χ^2 tests. Logistic regression was performed to assess the association between postpartum depressive symptoms, family cohesion, and adaptability, and odds ratios (ORs) and 95%CIs were calculated. In model 1, the associations between family cohesion, adaptability, and postpartum depressive symptoms were assessed without adjusting for covariates. Subsequently, variables that were significant in the univariate analysis or those that have been reported in previous studies as confounding factors were adjusted for in model 2. A two-tailed $P < 0.05$ was considered significant. All analyses were performed using Statistical Analysis System software (version 9.2; SAS Institute, Inc.,

Cary, NC, USA).

RESULTS

Characteristics and postpartum depressive symptoms of participants

As shown in Table 1, the age range of participants was 19–49 years, with an average age of 30 ± 4.30 years. Postpartum depressive symptoms were reported in 454 postpartum women for a prevalence rate of 31.4%. There were no significant differences between women with and without postpartum depressive symptoms in age ($\chi^2 = 2.07$, $P = 0.354$), education level ($\chi^2 = 2.65$, $P = 0.448$), mode of delivery ($\chi^2 = 0.177$, $P = 0.674$), gravidity ($\chi^2 = 4.004$, $P = 0.261$), or parity ($\chi^2 = 6.107$, $P = 0.107$). However, there was a significant difference in occupation between the two groups ($\chi^2 = 11.26$, $P = 0.046$).

Family cohesion and adaptability of postpartum women

The total scores for family cohesion and adaptability were significantly lower in the postpartum depressive symptoms group than in the group without postpartum depressive symptoms ($P < 0.001$; Table 2).

Association between different types of family cohesion and postpartum depressive symptoms

As shown in Table 3, the results of the univariate regression analysis showed that different types of family cohesion were associated with postpartum depressive symptoms (model 1, $P < 0.001$). In model 2, after adjusting for age, educational level, occupation, gravidity, parity, and mode of delivery, the disengaged type [adjusted OR (AOR) = 3.36, 95%CI: 1.91–5.91] and separated type (AOR = 1.97, 95%C: 1.34–2.90) had a higher risk of postpartum depressive symptoms than the connection type, whereas the enmeshed type (AOR = 0.38, 95%CI: 0.28–0.51) was a protective factor of postpartum depressive symptoms.

Association between different family adaptability types and postpartum depressive symptoms

The results of the univariate regression analysis showed that different family adaptability types were associated with postpartum depressive symptoms (Table 4, model 1, $P < 0.001$). After adjusting for age, educational level, occupation, gravidity, parity, and mode of delivery, rigid (AOR = 4.41, 95%CI: 3.02–6.43) and structured families (AOR = 1.88, 95%CI: 1.34–2.63) had a higher risk of postpartum depressive symptoms than flexible families, whereas chaotic families (AOR = 0.35, 95%CI: 0.24–0.51) protected against postpartum depressive symptoms.

DISCUSSION

We found that the prevalence of postpartum depressive symptoms was 31.6%, which is consistent with previous studies[15]. This indicates that postpartum depressive symptoms are an important perinatal mental health problem among. Furthermore, the levels of family cohesion and adaptability in the postpartum depressive symptoms group were significantly lower than those in the non-postpartum depressive symptoms group, which suggested that, when families are in the transition period between pregnancy and birth, high levels of cohesion and adaptability can enable family members to join forces, adjust strategies, and jointly help the mother cope with the various difficulties involved in raising children and the increase in costs. This, in turn, reduces the psychological pressure on women and lowers the risk of postpartum depressive symptoms. Previous studies have similarly found that higher family cohesion and adaptability reduce the prevalence of psychological disorders. For example, a survey conducted in 100 patients with terminal illnesses admitted to a palliative care ward in South Korea found that higher family adaptability reduced anxiety and depression in patients, whereas higher family cohesion resulted in lower rates of depression[25]. In a study of family cohesion and adaptability in youth at high clinical risk for psychosis, the youth and their mothers were reported to have lower adaptability and cohesion than their healthy control counterparts[26]. Moreover, a study on anger traits and somatization in junior college students in Shanghai, China, found that a high level of family cohesion and adaptability played a protective role, reducing the effects of anger characteristics on physical symptoms. They suggested that intervention measures that combine family cohesion, adaptive training, and depression treatment may be effective for patients with a high level of anger characteristics [27]. Taken together, we suggest that, to prevent and treat postpartum depressive symptoms, mental health workers specializing in women's mental health should focus on improving maternal family cohesion and adaptability.

Olson's theory of families, called "The Circumplex Model", suggests that family cohesion and adaptability have a curvilinear relationship with psychological and behavioral disorders. Excessively high or low cohesion and adaptability in the family are considered dysfunctional, and moderate cohesion and adaptability in the family model are regarded as beneficial[16,28]. Inadequate cohesion

Table 1 Characteristics of participants with and without postpartum depressive symptoms (*n* = 1446)

Characteristics	With postpartum depressive symptoms (*n* = 454)		Without postpartum depressive symptoms (*n* = 992)		χ^2	*P* value
	n	Percent	*n*	Percent		
Age (yr)					2.07	0.354
18–28	181	39.9	365	36.8		
29–34	217	47.8	481	48.5		
Over 35	56	12.3	146	14.7		
Educational level					2.65	0.448
Junior high school or below	67	14.8	122	12.3		
Senior high school	90	19.8	208	21.0		
College	131	28.9	315	31.8		
University and above	166	36.6	347	35.0		
Occupation					11.26	0.046
Leadership	6	1.3	26	2.6		
Professional and technical personnel	82	18.1	222	22.4		
Clerks	96	21.1	225	22.7		
Business and service personnel	107	23.6	237	23.9		
Unemployed / housewife	150	33.0	262	26.4		
Others	13	2.9	20	2.0		
Mode of delivery					0.177	0.674
Vaginal delivery	239	52.6	534	53.8		
Cesarean section	215	47.4	458	46.2		
Gravidity					4.004	0.261
1	201	44.3	389	39.2		
2	141	31.1	354	35.7		
3	71	15.6	154	15.5		
≥ 4	41	9.0	95	9.6		
Parity					6.107	0.107
1	269	59.3	521	52.5		
2	159	35.0	412	41.5		
≥ 3	26	5.7	59	6.0		

Table 2 Family cohesion and adaptability scores of postpartum women (*n* = 1446) (mean ± SD)

FACES II-CV	With postpartum depressive symptoms (*n* = 454)	Without postpartum depressive symptoms (*n* = 992)	*t* value	*P* value
Cohesion	66.78 ± 9.88	74.03 ± 8.60	14.16	< 0.001
Adaptability	48.62 ± 8.48	55.11 ± 7.39	14.77	< 0.001

FACES II-CV: Family Cohesion and Adaptability Scale.

leads to alienation and poor communication among family members, whereas excessive cohesion leads to family members lacking a sense of boundary and self-space. Furthermore, families with insufficient adaptability have more rigid family rules and an inability to adapt to environmental changes, whereas an excessive level of adaptability leads to confusion around family rules and a lack of organizational

Table 3 Association between types of family cohesion and postpartum depression (*n* = 1446)

Types of family cohesion	*n*	Rate	Model 1			Model 2		
			COR	95%CI	*P* value	AOR	95%CI	*P* value
Connected	410	28.40%	1.00			1.00		
Disengaged	78	5.40%	3.82	2.27-6.43	< 0.001	3.36	1.91-5.91	< 0.001
Separated	180	12.40%	2.03	1.42-2.89	< 0.001	1.97	1.34-2.90	< 0.001
Enmeshed	778	53.80%	0.4	0.31-0.53	< 0.001	0.38	0.28-0.51	< 0.001

Model 1: Univariate regression model, without adjusting for covariates; Model 2: Multivariate regression model, adjusted for age, occupation, educational level, gravidity, parity, and delivery mode. COR: Crude odds ratio; AOR: Adjusted odds ratio.

Table 4 Relationship between types of family adaptability and postpartum depressive symptoms (*n* = 1446)

Type of family adaptability	*n*	Rate	Model 1			Model 2		
			COR	95%CI	*P* value	AOR	95%CI	*P* value
Flexible	282	19.5%	1.00			1.00		
Rigid	428	29.6%	4.07	2.91-5.70	< 0.001	4.41	3.02-6.43	< 0.001
Structured	526	36.4%	1.83	1.35-2.48	< 0.001	1.88	1.34-2.63	< 0.001
Chaotic	210	14.5%	0.37	0.26-0.52	< 0.001	0.35	0.24-0.51	< 0.001

Model 1: Uncorrected model: univariate regression model, uncorrected confounding factors; Model 2: Corrected model: multivariate regression model, adjusted for age, occupation, education, gravidity, parity, and mode delivery. COR: Crude odds ratio; AOR: Adjusted odds ratio.

guidance, which is not conducive to the physical or mental health development of family members[29]. However, this model has also been questioned and criticized by some scholars, and several studies have reported inconsistent results. In a study conducted in South Korea on the correlation between adolescent behavioral problems and family cohesion and adaptability, results showed that the relationship between family cohesion, adaptability, and adolescent behavioral problems was linear rather than curvilinear. The study found that higher scores of family cohesion and adaptability were associated with a lower incidence of adolescent behavioral problems[30]. In addition, in a study on the relationship between psychological stress and family cohesion and adaptability in infertile couples, results showed that the relationship between family cohesion, adaptability, and psychological stress was also linear rather than curvilinear. They found that higher scores of family cohesion and adaptability were associated with less psychological pressure in couples with infertility[31].

We observed a linear relationship between family cohesion, adaptability, and postpartum depressive symptoms, where higher family cohesion and adaptability scores were associated with a lower risk of postpartum depressive symptoms. We speculate that this difference is related to the specific physiological stage of the postpartum period. Postpartum women often have poor self-functioning and are dependent on their surrounding environment[32,33]. Moreover, pregnant women in China often follow the custom of "confinement"[34,35], where postpartum women are taken care of at home for one month after giving birth and are not permitted to do housework or leave the house. High levels of cohesion and adaptability enable family members to offer crucial help to pregnant women, reducing psychological pressure and preventing the development of postpartum depression. The present findings are in line with the abovementioned studies. The findings here of a linear relationship rather than a curvilinear relationship between family cohesion, adaptability, and psychological and behavioral disorders may be related to the study population. Previous studies reporting curvilinear relationships were mainly conducted in general populations[16,36], whereas those reporting linear relationships were mainly focused on specific groups, such as adolescents, couples with infertility, and postpartum women. These groups often have weaker self-functioning and high dependence on their external environment and require significant support from their families to meet their needs to maintain psychological balance and prevent psychological and behavioral problems.

Limitations

The sample size of the present study was large, and we controlled for potential confounding factors. For example, interviews were conducted in the hospital by trained nurses, and a scale specifically developed for speakers of Mandarin was used for assessment, which offered reliability of the results.

However, the study also had limitations. For example, this was a single-center study. Furthermore, we used the EPDS to assess depressive symptoms without using the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) interviews to confirm diagnoses of depression. Indeed, research has suggested that self-reporting methods produce higher EPDS scores[37]. In addition, although we adjusted for several confounding factors, we did not control for other factors related to postpartum depressive symptoms, such as breastfeeding[38-40], intimate partner violence[5,15], and marital relationships[41,42]. We aim to include these factors in future studies using a hierarchical approach.

CONCLUSION

The present research showed that high family cohesion and adaptability prevented the development of postpartum depressive symptoms. For familial treatment of postpartum depression, family therapists may need to consider the physical and mental characteristics, customs, and cultures of postpartum women and appropriately adjust and enhance family cohesion and adaptability as much as possible to help prevent pregnant women from developing postpartum depression.

ARTICLE HIGHLIGHTS

Research background

Postpartum depression is the most common mental illness of mothers after childbirth, and the family environment is an important environmental factor affecting postpartum depression. Olson's theory of family cohesion and adaptability is a classic model to describe the level of family function. However, this model has not been tested in families of patients with postpartum depression.

Research motivation

The main focus was to explore the relationship between family cohesion/adaptability and postpartum depression symptoms. The key problem to be solved was how to investigate family cohesion and adaptability and postpartum depression symptoms and how to study the relationship between them. This research has great significance for future explorations into reducing the risk of postpartum depression.

Research objectives

The purpose of this study was to explore the relationship between family cohesion and adaptability and the risk of postpartum depressive symptoms.

Research methods

The clinical data of 1446 postpartum women with and without depressive symptoms were analyzed retrospectively. The Edinburgh Postpartum Depression Scale and the Chinese version of the Family Cohesion and Adaptability Scale II were used to evaluate depressive symptoms and family cohesion, respectively. Univariate regression analysis was used to evaluate the correlation between family cohesion and postpartum depression symptoms.

Research results

The prevalence of depression in postpartum women was 31.4%, and the family cohesion scores of this population were low. Univariate regression analysis showed that the risk of postpartum depression in detached and separated families was higher than that in connected families, while cohesion was a protective factor for postpartum depression. In addition, rigid and structured families had a higher risk of postpartum depression than flexible families, while chaotic families could prevent postpartum depression.

Research conclusions

This study showed that the prevalence of depression in postpartum women was 31.4%, and the family cohesion scores of this group were low. The higher the scores of family cohesion and adaptability, the lower the risk of postpartum depressive symptoms. Disordered families and cohesive families can prevent postpartum depression.

Research perspectives

Future research should investigate differences in family cohesion and adaptability in different types of families and their influence on postpartum depression according to the age, education, and the annual income of postpartum women.

FOOTNOTES

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Development of a protocol for videoconferencing-based exposure and response prevention treatment of obsessive-compulsive disorder during the COVID-19 pandemic

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Abstract

BACKGROUND

The existing literature indicates that psychotherapeutic treatment, especially exposure and response prevention (ERP) is efficacious in treating obsessive-compulsive disorder (OCD). The coronavirus disease 2019 pandemic adversely impacted many patients with OCD and disrupted their usual treatment. Moreover, the pandemic forced a global switch to telemental health (TMH) services to maintain the standards and continuity of care. Consequently, clinicians are increasingly using TMH-based psychotherapeutic treatments to treat OCD. However, several challenges have made it difficult for them to implement these treatments in the changed circumstances imposed by the pandemic.

AIM

To describe the formulation, implementation, feasibility, and usefulness of videoconferencing-based ERP (VC-ERP) treatment for OCD during the coronavirus disease 2019 pandemic.

METHODS

This prospective, observational study was conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (July 2020-June 2021). All patients with OCD were assessed using the home-based TMH services of the department. The VC-ERP protocol for OCD was the outcome of weekly Zoom meetings with a group of clinicians involved in administering the treatment. After a systematic evaluation of the available treatment options, an initial protocol for delivering VC-ERP was developed. Guidelines for clinicians and educational materials for patients and their families were prepared. The protocol was implemented among patients with OCD attending the TMH services, and their progress was monitored. The weekly meetings were used to upgrade the protocol

to meet the needs of all stakeholders. Feasibility and efficacy outcomes were examined.

RESULTS

All patients were diagnosed with OCD as a primary or a comorbid condition according to the International Classification of Diseases, 10th version criteria. Out of 115 patients who attended the services during the study period, 37 were excluded from the final analysis. Of the remaining 78 patients, VC-ERP was initiated in 43 patients. Six patients dropped out, and three were hospitalized for inpatient ERP. Eleven patients have completed the full VC-ERP treatment. One patient completed the psychoeducation part of the protocol. VC-ERP is ongoing in 22 patients. The protocol for VC-ERP treatment was developed and upgraded online. A large proportion of the eligible patients (n = 34/43; 79%) actively engaged in the VC-ERP treatment. Drop-out rates were low (n = 6/43; 14%). Satisfaction with the treatment was adequate among patients, caregivers, and clinicians. Apart from hospitalization in 3 patients, there were no other adverse events. Hybrid care and stepped care approaches could be incorporated into the VC-ERP protocol. Therefore, the feasibility of VC-ERP treatment in terms of operational viability, service utilization, service engagement, need for additional in-person services, frequency of adverse events, and user satisfaction was adequate. The VC-ERP treatment was found to be efficacious in the 11 patients who had completed the full treatment. Significant reductions in symptoms and maintenance of treatment gains on follow-up were observed.

CONCLUSION

This study provided preliminary evidence for the feasibility and usefulness of VC-ERP in the treatment of OCD. The results suggest that VC-ERP can be a useful option in resource-constrained settings.

Key Words: Videoconferencing; Exposure and response prevention; Obsessive-compulsive disorder; Telemedicine; COVID-19

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Core Tip: The coronavirus disease 2019 pandemic adversely impacted many patients with obsessive-compulsive disorder (OCD), compelling clinicians to increasingly use telemental health-based options rather than conventional psychotherapeutic treatments for OCD. This study described the implementation of a videoconferencing-based exposure and response prevention treatment protocol developed by an online group of clinicians during the pandemic. On prospective follow-up, 34 patients had either completed or were undergoing the treatment. The preliminary results showed that videoconferencing-based exposure and response prevention was a feasible and efficacious mode of treatment and may be a useful option for OCD, even in low-resource settings.

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INTRODUCTION

The existing literature regarding the treatment of obsessive-compulsive disorder (OCD) indicates that exposure and response prevention (ERP) or cognitive behavior therapy (CBT) that includes ERP is more effective in treating OCD than any other control or active psychotherapeutic treatment[1-5]. Moreover, the evidence also suggests that ERP is more efficacious than medication treatment of OCD, and the gains from treatment last longer. Nevertheless, combined treatment with medications and psychotherapy is more effective for severe OCD and is commonly used in routine clinical practice. However, despite the availability of evidence-based and effective psychotherapeutic treatments, very few patients have ready access to them. The rates of treatment-seeking are low among patients due to poor awareness, stigma, and inadequate engagement. The provision of ERP is also hampered by the shortage of professionals trained in administering ERP and skepticism among clinicians about ERP. Other hurdles include the longer duration and greater costs of ERP and the need to travel long distances for treatment. It has been proposed that telemental health (TMH) treatments may help in overcoming many

of these limitations of conventional ERP[3,4,6-8].

TMH-based psychotherapy has been used to treat OCD for more than three decades[6-10]. The older forms of such TMH treatments for OCD included computerized CBT and telephone-based CBT with or without therapist support. These methods were followed by videoconferencing-based ERP (VC-ERP) or CBT, with the earliest trials of these interventions starting to appear by the 1990s. The latest development in this field has been the advent of online psychotherapeutic interventions including internet-based CBT, web-based self-help groups, virtual reality-based ERP, and smartphone-based interventions. The existing evidence shows that TMH-based ERP/CBT for OCD leads to significant symptom reduction and improved functioning[9,11-14]. Treatment gains are often maintained for several months[8,9,11-13]. These treatments are feasible, acceptable, and cost-effective[8,10,12,14,15]. There appears to be no difference in efficacy between the TMH-based and in-person treatments[6,9,11,13,14], but this is not a consistent finding[7,8,10,16]. However, the evidence for these findings is relatively scarce and hampered by methodological inadequacies among the constituent studies[7,8,11,13,14]. Moreover, there are concerns about technological obstacles such as connectivity, safety, privacy, and confidentiality[7,10,17]. Lastly, clinicians are particularly dissatisfied with the inadequate treatment alliance and dropouts in TMH treatments[6,9,16].

The onset of the coronavirus disease 2019 pandemic negatively affected many patients with OCD[18-21]. There was an increase in patients with new-onset OCD and exacerbation of symptoms in those already suffering from OCD. However, studies have differed in their estimation of the impact of the pandemic on OCD. It seems that around two-thirds of the patients have been unaffected, whereas about one-third of patients have worsened[22]. The delivery of in-person ERP was also adversely affected because of the disruption in mental health services during the pandemic. While some studies found that ERP services were curtailed or that clinicians found it difficult to adapt to the changed circumstances[19,23], others reported no difference between the pre-pandemic and post-pandemic phases[22]. Nevertheless, the forced switch to TMH-based services during the pandemic in several countries[24] has meant that many clinicians are using TMH-based rather than conventional ERP for OCD[22,23,25].

A major lacuna in the existing literature on TMH-based psychotherapy for OCD is that most of the studies have been conducted in Western countries[13,14]. This applies to studies of internet-based CBT, VC-ERP, and other online interventions. Only a few studies of these interventions from Japan[26,27], Korea[28], and the Middle East[29] could be identified. In general, research on the efficacy of TMH in the treatment of psychiatric disorders from developing countries is limited, and reviews of the subject have not included trials on TMH-based treatment of OCD[30-32]. Apart from the lack of evidence, cultural acceptability of TMH-based treatments, their efficacy, and engagement with these treatments are also quite different in these countries. The situation in India is similar. Though VC-based TMH services were used in India before the pandemic and there was an upsurge in these services during it, there were large gaps in the delivery of these services[33,34]. Controlled trials on TMH-based psychotherapy of OCD are not available. Therefore, a new beginning had to be made. This study described the formulation and implementation of VC-ERP treatment for OCD during the pandemic and its current status in terms of feasibility and usefulness.

MATERIALS AND METHODS

This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Setting

The VC-ERP protocol was developed in the psychiatric unit of a multi-specialty hospital in north India. Patients with OCD attending the unit were already being treated with in-person ERP mostly on an inpatient basis. Inpatient ERP was associated with good short-term outcomes, but the long-term outcomes were unclear because of the high dropout rate after discharge[35]. Similar outcomes for inpatient ERP had been reported from another Indian center[36]. The department had also been running a home-based TMH service on a smaller scale since September 2018. This service was used for VC-based follow-up of patients who had completed in-person ERP. Following the shutdown of the outpatient clinics in March 2020, the home-based TMH service was upgraded and scaled up to cater to all outpatients. The features of this service have been described elsewhere[37]. This expanded platform allowed the delivery of VC-ERP based on the treatment protocol for in-person ERP.

VC-ERP for OCD

The in-person ERP protocol was modified to allow it to be delivered through the VC platform using the Zoom software. The use of VC was supplemented by WhatsApp video calls and messaging, phone calls (landline or smartphones), and e-mail. Virtual prescriptions sent by WhatsApp messages were used to convey advice regarding investigations and medications. The use of multiple digital modes of patient-clinician communication was consonant with the hybrid model of care, which had been recommended particularly during the pandemic[38]. This improves the flexibility and versatility of TMH-based care

and maintains its continuity by switching between different modes when one of them fails.

The modified VC-ERP protocol was developed based on feedback from a weekly Zoom group of clinicians actively involved in VC-ERP treatment for OCD. The group consists mainly of trainee psychiatrists, (post-MD) senior residents, and a consultant psychiatrist. Apart from group supervision of the trainees administering the treatment, the activities undertaken by this group have included carrying out a detailed review of the literature on ERP for OCD, TMH-based treatment options, and VC-ERP for OCD. Standardized guidelines for VC-ERP were prepared, and clinicians adhered to these standards of care. Educational materials for patients and their families were also prepared. The final protocol for VC-ERP is shown in Tables 1 and 2.

Differences between VC and in-person ERP

The differences between ERP by VC or by in-person treatment and the difficulties encountered during VC-ERP were the primary focus of many group discussions. The consensus views on this aspect are included in Table 3. These considerations provided the basis for the modifications made in the VC-ERP treatment protocol.

Modifications in technique required for conducting VC-ERP

Introductory education sessions with the patients and their caregivers were felt to be essential to improve their understanding and motivation for ERP. Although detailed psychoeducation sessions were carried out as a part of the ERP later, during this phase the objective was to provide enough information to ensure patient and caregiver cooperation with the process of assessment[39]. The contents of the brief information leaflet used for this purpose are depicted in Table 2.

A structured procedure for assessment was used. The clinician-administered version of the Yale-Brown Obsessive Compulsive Scale (YBOCS) was used to screen for different obsessions/compulsions as well as to rate the severity of obsessive-compulsive symptoms. The YBOCS is the most commonly used instrument for this purpose because of its reliable psychometric properties[1,4,13]. Standardized procedures such as those by Hawton *et al*[40] were used to conduct the behavioral analysis in the ABC format (antecedents, behaviors, consequences). Subjective units of distress were used to rate the severity of behaviors and also construct an ascending hierarchy of problem behaviors. The construction of the hierarchy was a key step in the process of planning for VC-ERP. Inputs were actively solicited from patients and caregivers during this stage. They were asked to keep a daily record of symptoms for about a week to make the hierarchy as comprehensive as possible. Google sheets or WhatsApp messages that could be regularly updated were used for this purpose. The assessment process often took up to 2 wk, but a prolonged and comprehensive assessment had many advantages such as increasing awareness about symptoms among the patients and caregivers, reducing their distress, and acquainting them with the VC-ERP treatment to follow. Finally, the hierarchies made were continuously upgraded during treatment based on the new information provided by patients or caregivers. Therefore, the process of assessment continued throughout the treatment.

A five-step approach to VC-ERP was used. These five steps of ERP were based on standard protocols of ERP or CBT[1,39,41-43]. Benson's relaxation technique[44] was the preferred mode of teaching relaxation exercises. The only other modification was that "processing" was used instead of cognitive restructuring. Processing involved discussing the patients' experiences and understanding of ERP and how this matched their expectations of the treatment[13,42]. Processing also allowed for discussions on the reality of the patient's beliefs, explanations about neutralization strategies, and suggestions about using more adaptive coping strategies. Modifications to the other components of the ERP are summarized in Table 4.

Outcomes of VC-ERP

The main focus of this study was on the feasibility outcomes including operational viability, service utilization, service engagement, need for additional services, frequency of adverse events, and treatment satisfaction and treatment preferences among patients, caregivers, and clinicians. The information about treatment engagement and the dropout rate was obtained from the medical records of patients who were offered ERP and either consented or refused the treatment. For all other outcomes, only patients who had agreed to undertake ERP and those who had completed or were actively engaged in the treatment were included. Patients were not interviewed separately for this part. Rather, the information was obtained from their treatment records. Therefore, any patient with incomplete treatment records was excluded. For the efficacy outcomes, only the 11 patients who had completed the entire VC-ERP were considered. Pre- and post-treatment YBOCS scores were extracted from their records to determine the efficacy of VC-ERP treatment. Information about the maintenance of gains post-treatment over 13 mo was also extracted from the treatment records.

Statistical analysis

The sample was characterized by using frequencies, means, and standard deviations. Loss to follow-up at any time was considered a dropout. Pre- and post-treatment comparisons were carried out using the Wilcoxon signed rank test.

Table 1 The treatment protocol for videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Components	Details
Detailed assessment	Establishing the diagnosis based on history and mental state examination Relevant investigations. Formulating a management plan consisting of medications and psychosocial treatment. The decision to start ERP was made following this assessment
Introductory psychoeducation[1]	Brief introductory education sessions with patients and designated caregivers with the help of a two-page written information leaflet for them
Standardized assessments	(1) YBOCS screening (2) YBOCS rating (3) Standardized behavioral analysis, *e.g.*, by Hawton *et al*[40] (4) Construction of ascending hierarchy of symptoms (according to the subjective units of distress on a 0%-100% scale)
Five-step ERP[2]	Psychoeducation, symptom monitoring, relaxation exercises, exposure and response prevention, and processing
Conduct of VC sessions[3]	All VC-ERP sessions were conducted at home, supervised by the clinician, and attended by the caregiver. WhatsApp messages or phone calls were used to convey advice regarding details of sessions, investigations, and medications
Additional strategies	Incorporation of additional techniques, *e.g.*, thought stopping with ERP for those with predominant obsessions
Relapse prevention	Continued follow-up through VC with constant re-emphasis on all components of the ERP. Booster sessions, if required upon completion of the initial VC-ERP treatment
Caregiver involvement	A family member designated as the primary caregiver was involved in the entire process of the VC-ERP treatment. The caregiver conducted homework sessions
Hybrid care	Hybrid treatment had two components (1) Employing a combination of VC-ERP sessions at home and in-person ERP sessions at the outpatient department (2) Employing multiple modes of patient-clinician communication such as VC, mail, text messages, and phones to augment in-person care

[1]Details in Table 2.

[2]These five steps of exposure and response prevention (ERP) were based on standard protocols of ERP or cognitive behavior therapy[1,39,41-43]. Psychoeducation imparted more detailed information about obsessive-compulsive disorder (OCD) including a cognitive-behavioral model of OCD. Apart from providing basic information about OCD, it attempted to correct common misconceptions. Psychoeducation also involved providing a clear rationale for ERP, information about the components and procedure for ERP, conduct of videoconferencing-based ERP sessions, and how ERP was expected to help. Patients and caregivers were taught to objectively monitor symptoms, thoughts, and distress during sessions and during the course of treatment. Standard formats for monitoring during videoconferencing sessions were developed. Google sheets or text messages that could be regularly updated were exchanged between clinicians and patients. The clinician carried out his/her own assessments, and feedback about progress of treatment was provided to the patient. Relaxation exercises, preferably using Benson's relaxation technique[44] were taught. It involved muscle relaxation, deep breathing, and the use of relaxation as a coping strategy. It was used to reduce anxiety and improve motivation for treatment. Standard techniques of ERP were used with certain modifications as explained in Table 4. During processing, the patients' experience of the sessions was discussed to enhance their understanding of ERP, examining the reality of their beliefs, and discussing more adaptive ways of coping[13,42].

[3]More details in Table 4.

ERP: Exposure and response prevention; VC-ERP: Videoconferencing-based exposure and response prevention; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Ethical considerations

This observational study was a part of a larger study on home-based TMH services for all patients[37]. The protocol was approved by the institute's ethics committee. Due to the restrictions imposed by the pandemic, verbal informed consent over the phone was allowed. As explained above, data regarding outcomes were obtained only from patients who had verbally consented to undertake ERP and had actively engaged in the process of treatment. However, patients were not contacted or assessed separately to determine these outcomes. Rather, all data regarding outcomes were extracted from routine medical and treatment records. Patient identities have not been revealed. Therefore, written informed consent from patients was not obtained for information about treatment outcomes. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

Table 2 Content of the brief introductory education session for videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Content
1 What is OCD? What are obsessions and compulsions in OCD?
2 How common is OCD?
3 How does the patient feel while experiencing the symptoms of OCD?
4 Why do patients develop OCD?
5 What are the types of treatment available?
6 What is the role of medications in treating OCD?
7 What is ERP and how does it work?
8 What is the need for ERP?
9 How will the VC-ERP sessions be conducted?
10 How long will the treatment take?

ERP: Exposure and response prevention; OCD; Obsessive-compulsive disorder; VC-ERP: Videoconferencing-based ERP for OCD.

Table 3 Problems with videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder and in-person and proposed solutions

	Difficulties with VC-ERP	Suggested solutions
Understanding and motivation of patients and caregivers	It was harder to explain the procedure to patients/caregivers. Motivation to engage in VC-ERP was often low. As a result, treatment engagement was variable	Early initiation of psychoeducation and the more frequent use of hybrid treatment
Difficulties faced during the assessment	The initial assessment took longer. Frequent interruptions due to poor network connectivity and the need to restart the process several times were common. Patients/caregivers often complained about the long period of assessment. Some patients became more anxious during the process	Educate patients/caregivers about the likely timeframes for assessment and treatment during the introductory psychoeducation sessions. Additional in-person sessions and administering benzodiazepines for short periods could help control anxiety
Conducting ERP sessions-patient-related and caregiver-related difficulties	These included variable cooperation, discomfort and hesitation, worry about confidentiality, indulging in neutralization strategies during sessions, preference for in-person visits, and problems with the timing and duration of the sessions	Shorter VC-ERP sessions (minimum of 30 min) and flexible scheduling of sessions (every 7-14 d). Ongoing education of patients and caregivers to ensure realistic expectations from VC-ERP
Conducting ERP sessions-clinician-related difficulties	Clinicians faced problems in sustaining their motivation, dealing with the additional burden of VC sessions and the need to adjust to a new medium	Training, supervision, and support for clinicians through regular group meetings
Technological difficulties	Poor connectivity, unavailability of proper equipment, user's unfamiliarity with technology, and time constraints	Modifications to the ERP procedure to make it more compatible with VC
Disadvantages	Group members conducting VC-ERP sessions rated it about three times as difficult compared to in-person ERP because of the problems encountered	A structured treatment package incorporating modifications in the treatment, ongoing education, and support for all users
Advantages	Group members agreed that VC-ERP had advantages such as greater access, convenience of carrying out sessions at home, and lesser likelihood of late disengagement if motivation could be ensured	The consensus was that though conducting VC-ERP may be more difficult than in-person ERP, the basic procedures and their implementation were similar

ERP: Exposure and response prevention; VC-ERP: Videoconferencing-based exposure and response prevention.

RESULTS

Participants

During the period of this study (July 2020-June 2021), the home-based TMH service was used to treat 3442 new and 12126 old patients. Of these, 115 new patients (3%) had a diagnosis of OCD as a primary or a comorbid condition according to the International Classification of Diseases, 10th version criteria. During subsequent follow-up, 1 patient whose diagnosis was changed from OCD to personality disorder was excluded; 28 patients had dropped out of treatment, and details regarding the status of 8 patients were not available. Therefore, 78 patients were included in the final analysis.

Table 4 Modifications in technique required for conducting videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

VC-ERP components	Modifications made to the VC-ERP
Detailed psychoeducation	Carried out using manuals in English and the local language for clinicians, patients, and caregivers. The content was simple, brief, and provided clear explanations. Psychoeducation sessions continued throughout the treatment
Monitoring of symptoms and progress	Simultaneous monitoring was carried out by the patients, caregivers, and clinicians through VC sessions, Google sheets, or WhatsApp messages that were regularly updated. Constant feedback about the progress of treatment was provided to the patient
Relaxation exercises	Benson's relaxation technique was preferred because of its brief and simple format. Autogenic training or modified Jacobson's progressive muscular relaxation exercises were taught if required. Written instructions in English and the local language and audio-visual aids for teaching were available for clinicians, patients, and caregivers
Duration of VC-ERP sessions	Though prolonged exposure is the goal because of its greater efficacy, it was quite difficult to have VC sessions of more than 30 min. Thus, the minimum duration was set at 30 min with the opportunity to prolong the sessions according to the patient's convenience
Frequency of VC-ERP sessions	The frequency of sessions varied from weekly sessions to one session every 10-14 d. Flexibility was essential in deciding the duration and frequency of sessions. Several other factors were considered, particularly patient/caregiver preferences, the stage of ERP, the severity of symptoms, and the availability of clinicians
Supervision of VC-ERP sessions	The patient's camera was not only focused on the patient but also covered a significant portion of the room so that clinician could detect any surreptitious compulsions or neutralizing acts. The camera was never switched off during the sessions
Engaging patients during the VC-ERP sessions	Clinicians, patients, and caregivers were all actively involved during the VC-ERP sessions. Every effort was made to minimize distractions. Neutralizing acts were noted and discussed later during processing. The clinician engaged with the patients at regular intervals to make sure that they were focusing on the treatment and to check the level of anxiety during sessions. However, constant talking was avoided because this might distract the patient
Ensuring patients' tolerance of anxiety	Patient comfort with the level of exposure and their ability to tolerate anxiety was of overriding importance. They were never forced to engage in something that made them uncomfortable during the ERP sessions. Rather, each step was undertaken after proper education and fully ensuring the patient's agreement and cooperation
The slower pace of VC-ERP	VC-ERP was expected to progress at a much slower pace than in-person ERP. This was explained to the patients and caregivers and usually did not present a problem
Privacy and confidentiality	Privacy was essential, and patients were informed about the people present in the room (*e.g.*, technicians) when the session was being conducted. The patient was only accompanied by the designated caregiver at home. Any recording was done only with the patient's explicit consent. All material relating to the treatment was stored securely
Safety	Patients were required to be accompanied by caregivers during the sessions. Anxiety levels were constantly monitored, and sessions were terminated if the patient was uncomfortable. If there were other concerns about the safety of the patient (*e.g.*, risk of self-harm or violence), closer monitoring was instituted for such highrisk situations. Caregivers were also educated to manage such high-risk situations. For persisting safety concerns including symptom exacerbations during VC-ERP, patients and family members were helped to attend outpatient or emergency services
Treatment of comorbidities	Other modalities such as medications or occasionally ECT were used to treat primary or secondary comorbidities. The VC-ERP was adapted to meet the needs of patients with comorbid symptoms. Techniques utilized included temporarily suspending the sessions when comorbid symptoms increased, offering increased support at this time using the VC platform, promoting greater involvement of caregivers, and combining VC sessions with in-person sessions
Using hybrid modes of treatment	Hybrid care involved conducting some of the initial ERP sessions on an in-person basis and the later sessions by utilizing VC. Similarly, for each new step of the hierarchy, the initial session was an in-person one followed by VC sessions. This often mitigated the problems of poor understanding and variable motivation noted in exclusive VC-ERP treatment. Requests from patients and caregivers for in-person sessions were catered to as far as possible
Self-exposure	In exceptional instances when caregivers were not available, therapist-guided self-exposure was tried. A greater level of patient motivation was required for self-exposure and the pace of ERP was slower

ERP: Exposure and response prevention; VC-ERP: Videoconferencing-based exposure and response prevention. ECT: Electroconvulsive therapy.

Patient profiles

Out of 78 patients, 38 were men and 40 were women. In general, patients seen during the pandemic were more likely to be older, married, better educated, and from higher-income families living near the hospital[37]. However, many patients were barely literate, impoverished, and from distant, rural locations. Three patients had late-onset OCD. Twenty-one patients had a comorbid psychiatric illness. OCD as a primary condition included the following comorbidities: single depressive episode (n = 6), recurrent depressive disorder (n = 4), dysthymia (n = 1), agoraphobia (n = 1), hypochondriasis (n = 1), and impulse control disorder (n = 1). OCD as a secondary comorbidity was present in schizophrenia (n = 3), bipolar disorder (n = 2), dementia (n = 1), and traumatic brain injury (n = 1). Most patients were on pharmacological treatment for OCD and comorbid conditions.

VC-based ERP for OCD: feasibility, acceptability, and efficacy

Tables 5 and 6 provide these details.

VC-ERP was considered in the majority of patients with OCD, but because of different reasons only about half of them (55%) started VC-ERP. Of the 43 patients who started VC-ERP, 6 dropped out early and 3 had to be hospitalized for inpatient ERP. Thus, a large proportion of the eligible patients (n = 33/43; 77%) had completed the full treatment (n = 11) or were currently undergoing VC-ERP (n = 22). One patient improved following the initial sessions and did not have to complete the entire treatment. Hybrid treatment was more commonly used by many of these patients (n = 20) once the outpatient services resumed. Most patients and caregivers considered this to be a better option and preferred hybrid care.

Feasibility outcomes among the 34 patients engaged in VC-ERP showed that it was possible to implement the treatment in usual clinical settings. Drop-out rates were low (n = 6/43; 14%). Apart from the 3 patients (9%) with severe OCD who did not respond to VC-ERP and required hospitalization, there were no other adverse events. The number of patients treated with VC-ERP in a year was more than those who had received inpatient ERP for a year during the pre-pandemic period. Satisfaction with the treatment was adequate among patients, caregivers, and clinicians. Therefore, the feasibility of VC-ERP treatment in terms of operational viability, service utilization, service engagement, need for additional in-person services, frequency of adverse events, and user satisfaction was adequate.

The 11 patients who completed the entire treatment had moderate levels of OCD for several years. VC-ERP led to significant reductions in the YBOCS scores on completion. Treatment gains have been maintained in these patients on follow-up for a year after completing the VC-ERP. More than half of them (54%) had comorbid conditions, but this did not affect their improvement with VC-ERP.

DISCUSSION

TMH-based services are efficacious and suitable alternatives to in-person care and have proved to be particularly useful during the pandemic. By promoting ready access to psychiatric care, they can remove several barriers associated with conventional services, enhance satisfaction among users, and empower the underserved population from remote areas[24,31,32].

The efficacy, advantages, and disadvantages of VC-based ERP for OCD

Several reviews[6-10] and meta-analyses[11,13] of TMH-based treatments for OCD have found that VC-based treatment is useful, but they have only included a few trials of VC-ERP for OCD. Similarly, meta-analyses[25,45,46] and reviews[17,47-50] that have found VC-based treatments to be effective for psychiatric disorders have included a limited number of VC-ERP studies of OCD. This is not surprising because there are only three randomized-controlled trials (RCTs) of VC-ERP in OCD[51-53]. A fourth RCT of VC treatment for anxiety and mood disorders included 4 patients with OCD[54]. These RCTs have shown that VC-ERP is more efficacious than neutral or active control treatments and equal in efficacy to in-person ERP. Treatment gains are maintained for several months, and VC-ERP had a more positive impact on the treatment alliance and patient engagement. Open trials have similarly shown that VC-ERP is an effective, feasible, acceptable, and cost-saving treatment, which can be used to supplement in-person ERP[27,55-58]. However, the RCTs have small sample sizes and are of brief duration. Therefore, without properly conducted RCTs with non-inferiority or equivalence designs, the current evidence in favor of VC-ERP for OCD cannot be considered adequate[59].

Like other TMH-based treatments, VC-ERP has several advantages compared to in-person ERP[7,13,17,50,52]. It leads to wider dissemination of ERP and greater patient access to evidence-based ERP. Home-based ERP allows greater flexibility, greater involvement of family members in ERP, and more opportunities to address the negative attitudes or accommodations by the family. It can be cost-effective because it reduces travel costs and absence from work. Since patients receive treatment at home, the stigma associated with seeking psychiatric treatment is lessened. However, VC-ERP has its challenges. It is heavily dependent on external factors such as technological infrastructure, internet penetration and affordability, network connectivity, and the user's familiarity with technology. Patient and family motivation might be poor, forging effective treatment alliances may be difficult, and supervision and monitoring may not be optimal[50,52,56].

VC-based ERP for OCD vs internet-based CBT

Currently, there seems to be a greater emphasis on delivering online or internet-based ERP or CBT for OCD particularly in high-income countries[9]. The two types of treatment have their advantages and disadvantages. Internet-based CBT has a broader evidence base and the number of trials including RCTs is much more than those of VC-ERP[10,11-14]. Its efficacy is comparable to in-person CBT. Internet-based CBT is particularly useful as an initial option for mild or moderate OCD. Moreover, it is more readily accessible and offers a wider choice of techniques and varying levels of clinician assistance. The treatment is efficacious and cost-effective even with low levels of clinician support[15]. Moreover, greater levels of clinician support can help minimize dropouts, and treatment gains are usually

Table 5 Details of videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Patients	Number	Comments/details
Patients with OCD attending the home-based TMH services during the study-period	115	This was 3% of all new outpatients and represented an increase in the number of such patients compared to the period before the pandemic
Patients available for analysis	78	ERP not considered (n = 17; 15%); improved with medications and did not require ERP (n = 2); refused ERP (n = 3); VC-ERP yet to be initiated (n = 13)
Patients in whom VC-ERP was initiated/early dropouts	43	Six patients dropped out from VC-ERP treatment. (Dropout rate 14%)
Improvement after initial treatment	1	One patient improved after initial psychoeducation and regular relaxation exercises and was not required to complete the entire VC-ERP treatment
Transition to hybrid care	20	Hybrid care became easier once the outpatient services resumed in December 2021
Transition to inpatient ERP	3	VC-ERP was followed by inpatient-based ERP because of severe OCD and non-response to VC-ERP.
Patients who have undergone/are undergoing VC-ERP	33	VC-ERP has been completed in 11 patients and is ongoing in 22 patients

ERP: Exposure and response prevention; OCD: Obsessive-compulsive disorder; VC-ERP: Videoconferencing-based exposure and response prevention; TMH: Telemental health.

Table 6 Efficacy of videoconferencing-based exposure and response prevention treatment for obsessive-compulsive disorder

Age	Sex	Marital status	Residence	Comorbidity	Duration of OCD	Baseline YBOCS score	YBOCS score at completion
Mean: 31.27 (SD: 9.65) yr, range: 22-56 yr	Men: 9; Women: 2	Single: 8; Married: 3	Urban: 9; Rural: 2	OCD primary disorder: 7 (depressive disorder: 2); OCD secondary disorder: 4 (schizophrenia: 3; bipolar disorder: 1)	Mean: 6.90 (SD: 6.48) yr, range: 1-25 yr	Mean: 25.45 (SD: 5.63), range: 17-36	Mean: 4.27 (SD: 4.22)[1], range: 0-13

[1]Significant reduction in Yale-Brown Obsessive-Compulsive Scale scores; Z = 2.936; P < 0.01 (using the Wilcoxon signed rank test).
OCD: Obsessive-compulsive disorder; YBOCS: Yale-Brown Obsessive-Compulsive Scale; SD: Standard deviation.

enduring.

Despite these advantages, there is no difference in efficacy between VC-ERP and internet-based treatments[13]. Indeed, some of the evidence seems to indicate that VC-ERP may be more efficacious than internet-based treatments[45,60]. Moreover, VC-ERP resembles the "gold-standard" in-person ERP more closely than internet-based ERP[13,16,17,45,46]. Since VC-ERP is conducted at home, it has the advantage of greater convenience, more chances of the behavioral gains generalizing to natural settings, increased involvement of the family, and a better insight into the patient's home environment[6,16,17,45,50]. Some reviews also suggest that VC-ERP is more suitable for those with severe OCD[8,9] and patients from remote locations[16,45-47,50], whereas internet-based treatments are more useful in milder OCD and for people with better access to the internet[8-10]. Lastly, the main advantage of VC-ERP seems to be the greater therapeutic contact it provides particularly in comparison to internet-based treatments with minimal therapist contact. There is considerable evidence to indicate that higher levels of therapeutic contact are associated with greater efficacy of TMH-based treatments for OCD[7,9,14,61,62].

The choice of VC-ERP in this study was influenced by these considerations along with the prior experience of in-person ERP in the department, the availability of a home-based platform for VC-ERP, and the unavailability of internet-based treatments.

Findings of the present study and its limitations

Being a preliminary report, this study had several obvious limitations. It was largely a descriptive account of the development and implementation of VC-ERP for OCD from a relatively under-resourced setting. The number of patients who had completed the treatment was very small, and all data related to the efficacy of VC-ERP are therefore prone to a high risk of bias. This risk is increased further because patients were not randomized to VC-ERP treatment, and there was no control group. A selection bias toward better-motivated patients is also possible. Since this was a naturalistic observational study, it was not possible to control for confounding factors such as the effect of pharmacological treatment or comorbid conditions.

Nevertheless, some of the findings were encouraging and could have some implications for further efforts in this area. The principal focus of this study was to describe the process of developing a protocol for VC-ERP treatment of OCD during the pandemic. Due to the restrictions imposed by the pandemic the entire process of development and subsequent implementation had to be carried out online. The primary aim of the study was to examine the operational viability and feasibility of conducting VC-ERP according to the treatment protocol developed in this study. The examination of these outcomes among 34 patients who had completed the treatment or were actively engaged in it indicated that the VC-ERP protocol was a feasible and viable means of treating OCD.

The VC-ERP treatment provided access to a larger number of patients who could benefit from ERP. Dropout rates were low and adverse events were relatively rare. The treatment was acceptable to patients, caregivers, and clinicians, and the levels of satisfaction were adequate. Since this was a naturalistic observation study among patients from routine care settings, these results can be generalized to other patients from similar clinical settings. Moreover, since the treatment was conducted in a low-resource setting of a developing country like India, these results could be particularly relevant for countries with similar resource constraints. Although the treatment was mostly conducted during the pandemic, the findings showed that it was feasible to implement the treatment even after the pandemic had subsided. Moreover, such naturalistic studies also fulfil the pressing need to conduct VC-ERP trials for OCD in real-world settings[9,16,60].

Its findings corresponded to the recent studies of OCD, which indicated that VC-ERP may be equally effective in routine treatment settings[22,63,64]. The use of hybrid treatment both in terms of multiple platforms for hosting VC-ERP and combining it with in-person care offers a greater degree of flexibility and has the potential for greater effectiveness[15,16,38,45,50]. Similarly, this study found that hybrid care was considered to be more advantageous and preferred by patients, caregivers, and clinicians. Another unexpected gain of the VC-ERP treatment was the opportunity to incorporate stepped care into the treatment protocol. Stepped care refers to the use of low-intensity treatments such as internet-based CBT for patients with less severe OCD with the option to transition to more intensive treatments if the illness is more severe. It has been advocated for a long time but is being re-emphasized because of the wide range of TMH-based treatments currently available for OCD[7,9,13,14,16]. In this study patients with milder OCD improved after the initial sessions, while many with more severe OCD moved on to hybrid care, and a few with the most severe illnesses could move on to inpatient ERP when VC-ERP failed. This was consistent with the stepped care approach.

The findings regarding the efficacy of VC-ERP among 11 patients who had completed the full treatment were very preliminary and had several limitations that have been listed above. Nevertheless, they did suggest that the VC-ERP treatment of this study was an effective means of managing OCD in terms of significant symptom reduction and maintenance of gains post-treatment. The extent of improvement was similar to other Indian studies of inpatient ERP for OCD[35,36]. However, the long-term outcome of VC-ERP was likely to be better because of the improved treatment engagement and follow-up with the treatment. These results were also in line with much of the existing evidence on the efficacy of VC-ERP from RCTs[51-54] and open trials[27,55-58]. Lastly, the findings suggested that VC-ERP treatment could be useful for a population with moderately severe OCD and high rates of comorbidity. Though most of the evidence appears to indicate that VC-ERP is ineffective in treating comorbid depression[7,11,22], some studies have shown that it is equally effective in those with comorbid conditions[22,64].

CONCLUSION

In conclusion, the present study has shown that despite many barriers it is possible to develop a structured form of VC-ERP for OCD that is feasible and acceptable to the users. The findings, though preliminary, suggest that VC-ERP could be a viable option for the treatment of OCD in low- and middle-income countries where the treatment gap for OCD is greater and TMH services are relatively underdeveloped. However, much more will need to be done to improve this treatment and prove its efficacy before it can be integrated into the wider system of mental healthcare in these countries.

ARTICLE HIGHLIGHTS

Research background

The existing literature indicates that exposure and response prevention (ERP) is efficacious in treating obsessive-compulsive disorder (OCD). However, despite the availability of such effective psychotherapeutic treatments, very few patients have ready access to them. Telemental health (TMH) treatments may help in overcoming these limitations of conventional ERP.

Research motivation

The coronavirus disease 2019 pandemic adversely impacted many patients with OCD, compelling clinicians to increasingly use telemental health-based options rather than conventional psychotherapeutic treatments for OCD. However, research on the efficacy of TMH in the treatment of psychiatric disorders from developing countries is limited, and trials on TMH-based treatment of OCD are rare. This study from India described the formulation and implementation of videoconferencing-based ERP (VC-ERP) treatment for OCD during the pandemic and its current status in terms of feasibility and usefulness.

Research objectives

To describe the formulation of a treatment-protocol for VC-ERP developed by an online group of clinicians, to describe the implementation of the protocol, and to examine the feasibility and usefulness of the VC-ERP treatment for OCD during the pandemic and after it.

Research methods

This prospective, observational study was conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (July 2020-June 2021). All patients with OCD were assessed using the home-based TMH services of the department. The VC-ERP protocol for OCD was the outcome of weekly Zoom meetings with a group of clinicians involved in administering the treatment. The protocol was implemented among patients with OCD attending the TMH services and upgraded to meet their needs. Feasibility and efficacy outcomes were examined.

Research results

One hundred and fifteen patients with OCD attended the TMH services during the study period; 37 of these were excluded. Of the remaining 78 patients, VC-ERP was initiated in 43 patients. Six patients dropped out, and 3 patients were hospitalized for inpatient ERP. Eleven patients have completed the full VC-ERP treatment. One patient improved following the initial sessions and did not have to complete the entire treatment. VC-ERP is ongoing in 22 patients. The feasibility of VC-ERP treatment in terms of operational viability, service utilization, service engagement, need for additional in-person services, frequency of adverse events, and user satisfaction was adequate. Significant reductions in symptoms and maintenance of treatment gains on follow-up were observed in 11 patients who completed the entire treatment.

Research conclusions

This study provided preliminary evidence for the feasibility and usefulness of VC-ERP in the treatment of OCD. It suggested that VC-ERP could be a viable option for the treatment of OCD in low- and middle-income countries with a greater treatment gap for OCD and underdeveloped TMH services.

Research perspectives

Further research is needed to improve the VC-ERP treatment and prove its efficacy before it can be integrated into the wider system of mental healthcare.

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FOOTNOTES

Author contributions: Kathiravan S and Chakrabarti S were involved in preparing the study protocol and conducting the review of the literature; Kathiravan S collected the data about patient treatment; Kathiravan S and Chakrabarti S were both involved in analyzing the data and preparing the manuscript; All authors have approved the final version of the manuscript for submission.

Institutional review board statement: This observational study was a part of a larger study on home-based TMH services for all patients[37]. The protocol was approved by the institute's ethics committee. Due to the restrictions imposed by the pandemic, verbal informed consent over the phone was allowed. Copies of the approval from the ethics committee have been uploaded.

Informed consent statement: This observational study was a part of a larger study on home-based TMH services for all patients[37]. The protocol was approved by the institute's ethics committee. Due to the restrictions imposed by the pandemic, verbal informed consent over the phone was allowed. As explained above, data regarding outcomes were

obtained only from patients who had verbally consented to undertake exposure and response prevention and had actively engaged in the process of treatment. However, patients were not contacted or assessed separately to determine these outcomes. Rather, all data regarding outcomes were extracted from routine medical and treatment records. Patient identities have not been revealed. Therefore, written informed consent from patients was not obtained for information about treatment outcomes. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

Conflict-of-interest statement: None of the authors have any potential conflicts of interest to report. Details have been provided in the conflict-of-interest statement format.

Data sharing statement: Data regarding the study are available from the corresponding author (subhochd@yahoo.com) upon reasonable request.

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CASE REPORT

Major depressive disorder is correlated with the mitochondrial *ND1* T3394C mutation in two Han Chinese families: Two case reports

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Abstract

BACKGROUND

Major depressive disorder (MDD) is the most frequent reason of disabled people in the world, as reported by the World Health Organization. However, the diagnosis of MDD is mainly based on clinical symptoms.

CASE SUMMARY

The clinical, genetic, and molecular characteristics of two Chinese families with MDD are described in this study. There were variable ages of onset and severity in depression among the families. Both Chinese families had a very low prevalence of MDD. The mitochondrial genomes of these pedigrees were sequenced and indicated a homoplasmic T3394C (Y30H) mutation, with the polymorphism located at a highly conserved tyrosine at position 30 of *ND1*. The analysis also revealed unique sets of mitochondrial DNA (mtDNA) polymorphisms originating from haplogroups M9a3 and M9a.

CONCLUSION

This finding of the T3394C mutation in two unrelated depressed patients provides strong evidence that this mutation may have a part in the etiology of MDD. However, In these two Chinese families having the T3394C mutation, no functional mtDNA mutation was observed. Therefore, T3394C mutations are related with MDD, and the phenotypic manifestation of these mutations may be affected by changes in nuclear genes or environmental factors.

Key Words: Major depressive disorder; Mitochondrial DNA; *ND1*; Mutation; Haplogroup; Chinese; Case report

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Core Tip: We characterized two Chinese families with suspected maternal transmission of major depressive disorder at the clinical, genetic, and molecular levels in the present study. Molecular investigation revealed that the T3394C mutation in the *ND1* gene was present in these Chinese families.

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INTRODUCTION

Major depressive disorder (MDD) is a frequent dangerous human disease, which severely impairs the normal life and work of patients and causes a heavy burden on their family and society. In 2008, the World Health Organization rated it as the third leading cause of worldwide disability, and by 2030, it is expected to lead the list[1]. Despite its high incidence and prevalence, clinical symptoms are the primary basis for a diagnosis of MDD, and there is little evidence at the molecular level[2]. In addition, current drug therapy for MDD is not effective, with only 27% of patients in remission after the first treatment and 67% in remission after four complete treatments[3]. These considerations imply that the currently available antidepressants that target the monoaminergic system are insufficient for therapeutic use. In evaluating new therapeutic approaches, specific biomarkers should be identified that objectively determine the pathology involved in MDD, and relevant molecular targets might be revealed[4].

Mitochondrial DNA (mtDNA) is a 16.6 kb circular molecule that is maternally transferred and found within the mitochondrion[5]. Mitochondria can be considered "power generators" because they transform oxygen, energy substrates (proteins, carbohydrates, and lipids), and other substances into adenosine triphosphate[6]. In major psychiatric diseases, significant changes in the mitochondrial count, shape and electron transport activity in neurons are accompanied by an increase in mitochondrial DNA polymorphism, deletion and mutation, suggesting that defects in the mitochondria might be a primary cause of MDD[7,8]. Munakata *et al*[9] sequenced the whole mitochondrial genome of white blood cells from a family in which a proband was suspected of maternal inheritance of borderline personality disorder, MDD, suicide and other psychiatric disorders. The patient was identified as having both MDD and epilepsy. Comparing the proband sequence to the standard human mtDNA sequence, the authors identified 34 base changes. From the mtDNA sequence, it is possible to detect comprehensive subhaplogroups, new mutations, and common single nucleotide polymorphisms. It is also possible to determine private mutations in mtDNA through resequencing, especially if they are homoplasmic, which contributes to the variance between individuals in mtDNA composition[10].

This study aimed to characterize clinical, genetic, and molecular characteristics of two Chinese families with possible maternally transmitted MDD. The T3394C mutation in the *ND1* gene in these Chinese families was identified through molecular analysis. We employed polymerase chain reaction (PCR) amplification of fragments covering the full mitochondrial genome and subsequent DNA sequence analysis to shed insight on the significance of the mitochondrial haplotype in the phenotypic expression of the T3394C mutation in two Chinese families.

CASE PRESENTATION

Chief complaints

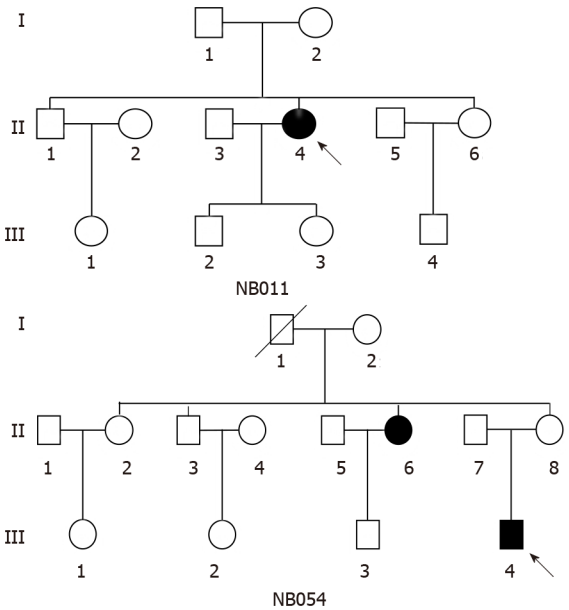
We ascertained two Han Chinese families (Figure 1) through the Psychiatric Clinic of Ningbo Kangning Hospital, Zhejiang. The Ningbo Kangning Hospital Ethics Committee approved the protocol, and obtaining clinical assessments and collecting blood samples from all family members required informed consent. In-depth interviews were conducted with members of these pedigrees to discover family and personal medicinal records of major depressive disorder and other medical abnormalities. To check for mtDNA alterations, we collected 167 DNA samples from healthy Chinese people who served as controls.

In family NB011, as shown in Table 1, the proband (II-4) complained of depression and visited the Psychiatric Clinic at Ningbo Kangning Hospital at the age of 62. She struggled with MDD approximately 12 years prior. The Hamilton depression rating scale (HDRS) showed a score of 24 and no

Table 1 Summary of clinical molecular data for two probands carrying the *ND1* T3394C mutation

Subject	Gender	Age at testing (yr)	Age at onset (yr)	First episode	History of suicide attempt	HDRS	Level of depression	mtDNA haplogroup
NB011-II-4	F	62	50	N	N	21	Moderate	M9a3
NB054-III-4	M	20	12	N	Y	39	Severe	M9a

HDRS: Hamilton depression rating scale.



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Figure 1 Two Chinese pedigrees with major depressive disorder. Patients are indicated by filled symbols. The arrow denotes the probands.

history of suicide attempt. She exhibited the classic clinical features of MDD. The psychiatric examination found no other abnormalities. In addition, no further significant medical background was discovered. The family was from East China's Zhejiang Province. None of the remaining seven matrilineal relatives displayed MDD.

In the NB054 pedigree, the proband (III-4) visited the Psychiatric Clinic at Ningbo Kangning Hospital upon reaching the age of 20. He struggled with MDD 8 years prior. The HDRS showed a score of 39 and a history of suicide attempt. Thus, he had classic symptoms of clinical features of MDD. no further significant medical background was discovered. The family was also from Zhejiang Province in Eastern China. Clinical testing and additional research into II-6's family history confirmed that she had MDD. Other matrilineal relatives did not show signs of MDD.

History of present illness

In addition, there was no indication that any member of these families had an alternative recognized etiology for MDD.

History of past illness

Comprehensive family medical histories of these individuals showed no other clinical abnormalities existed in these people's families, such as diabetes, hearing loss, or vision problems.

Psychiatric examinations and evaluation by the Hamilton depression rating scale

The diagnosis of MDD for the probands was developed by utilizing structured clinical interviews[11] and was confirmed by a separate diagnostic examination conducted by a licensed psychiatrist. Depressive symptom intensity in patients with MDD was measured by the HDRS[12]. The probands with MDD got a minimum HDRS score of 17 on 17 items. The severity of MDD was determined by HDRS as follows: normal < 7; mild = 7-17; moderate = 17-24; severe > 24. The probands of MDD were not included if they had any of the following conditions according to DSM-IV: (1) Abuse of alcohol or drugs within the previous six months; (2) bipolar disorder; and (3) post-traumatic stress disorder or a history of an eating disorder within the previous month of study enrollment.

Laboratory examinations

Mitochondrial genome mutational analysis: Utilizing Puregene DNA Isolation Kits (Gentra Systems), genomic DNA was extracted from the subjects' entire blood. As previously stated, L- and H-strands oligonucleotide primer sets were used to amplify the whole mitochondrial genomes of the two probands by PCR in 24 overlapping fragments[13]. Each purified fragment was examined using direct sequencing on an ABI 3100 automated DNA sequencer utilizing a Big Dye Terminator Cycle sequencing reaction kit. Consensus Cambridge sequence was matched to these sequence findings (GenBank accession number: NC 012920)[14]. The Seqweb program GAP (GCG) was used for DNA and protein sequence alignments. Genomic DNA from Chinese controls were used as templates, we amplified segments spanning the required sites by PCR and sequenced the resulting PCR products to determine the allele frequency of the T3394C mutation in the *ND1* gene.

Phylogenetic analysis and haplogroup analyses: Homo sapiens[14], mouse[15], bovine[16], and Xenopus laevis[17] mitochondrial DNA sequences were utilized in the interspecific study. By comparing the four animals, the conservation was evaluated. The complete mtDNA sequences of the two Chinese probands with the T3394C mutation were allocated to the Asian mitochondrial haplogroups as per the nomenclature of mitochondrial haplogroups[18,19].

Mitochondrial DNA analysis: The mitochondrial genome of these probands for mutations was analyzed to determine the molecular basis of MDD. PCR was used to amplify the whole genome fragments of mitochondria that were then sequenced from the samples of these probands. Substances with MDD have been shown to carry a T-to-C transition at position 3394 (T3394C) in the *ND1* gene, which causes the amino acid tyrosine to be replaced by histidine (Y30H) at position 30[20]. Figure 2 shows that the tyrosine at ND1 position 30 is significantly preserved across 27 different species. Leber's hereditary optic neuropathy (LHON) has been linked to this mutation in 3 Chinese families[21] and 1 Finnish family[22], as well as metabolic diseases[23], and deafness[24] in 1 Chinese family. From a sample of 167 unrelated Chinese control people, we know that one (20-year-old man) carries the T3394C mutation based on allele frequency analysis.

Besides the identical T3394C mutation (Table 2), these individuals displayed unique mtDNA polymorphisms. Other nucleotide variations in these mitochondrial genomes include 12 documented variations in the D-loop, three recognized variations in the *12S rRNA* gene, 1 recognized variation in the *16S rRNA* gene, 14 recognized silent variants, and 11 (2 novel/9 known) nonsense mutations in the polypeptide-encoding genes. These nonsense mutations are T4216C (T304H) in the *ND1* gene; G4491A (V8I) in the *ND2* gene; A8701G (T59A), TG8728T (T68G), A8860G (T112A) and A9136G (I204V) in the *A6* gene; A10398G (T114A) in the *ND3* gene; A14417G (V86A) in the *ND6* gene; and C14766T (T7I) and A15326G (T194A) in the *Cytb* gene. There were 31 mutations that were carried by both probands. Phylogenetic analysis of these RNA and polypeptide variations and sequences from other taxa, such as mice[15], cattle[16], and Xenopus laevis[17], was used to assess these variants further. Nevertheless, with the exception of T3394C, none of these variations shown evolutionary conservation. The mtDNA sequence variants of two Chinese relatives were used to identify their haplogroup affiliation of each mtDNA using the nomenclature of mitochondrial haplogroups[18,19]. The mtDNA of pedigrees NB011 and NB054 correspond, respectively, to the Eastern Asian haplogroups M9a3 and M9a.

FINAL DIAGNOSIS

The described patients are all ultimately diagnosed with MDD.

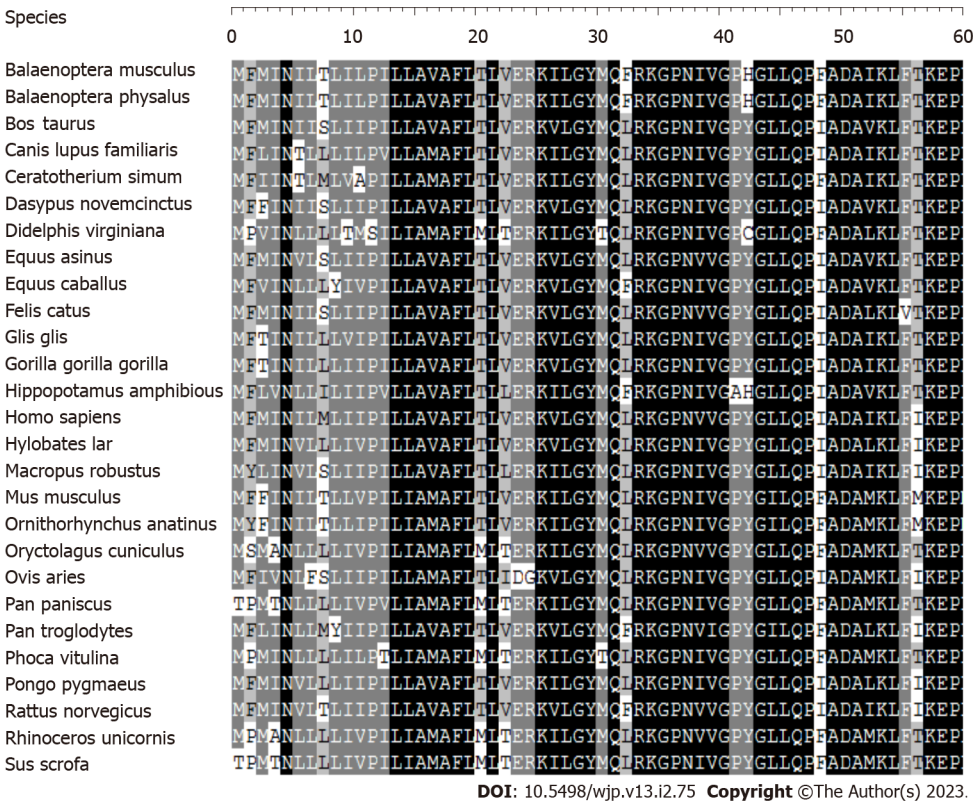
DISCUSSION

In this investigation, the clinical, genetic, and molecular characteristics of two Chinese families with MDD were determined. MDD had a distinct clinical phenotype and solely existed in the maternal lineage in the two families, prompting us to speculate that mtDNA may be the molecular foundation of MDD. Complete mitochondrial genome sequence study of the two pedigrees revealed different mtDNA polymorphisms except for the same T3394C (Y30H) mutation in the *ND1* gene. The *ND1* gene is the central component of the 45 subunits of complex I, and the T3394C mutation caused a shift from tyrosine to histidine (Y30H) at position 30[25,26]. Actually, the hydroxyl group on Y30 of ND1 interacts electrostatically with the side chain of E4 and the carbonyl group on M1 of NDUFA1[26,27]. Consequently, the T3394C mutation may disturb the interactions among ND1 and NDUFA1, consequently affecting the structure and function of complex I[28]. Leber's optic neuropathy[21,22], metabolism disorders[23] and deafness[24] are only some of the additional clinical problems linked to the T3394C mutation.

Table 2 mtDNA mutations in two Chinese pedigrees with major depressive disorder

Gene	Positon	Replacement	Conservation[a] (H/B/M/X)	CRS[b]	NB011	NB054	Previously reported[c]
D-loop	73	A-G		A	G	G	Y
	146	T-C		T	C	C	Y
	153	A-G		A	G	G	Y
	263	A-G		A	G	G	Y
	309	C-CCT		C		CCT	Y
	310	T-C		T	TC	C	Y
	489	T-C		T	C	C	Y
	16223	C-T		C	T	T	Y
	16234	C-T		C	T	T	Y
	16291	C-T		C	T		Y
	16316	A-G		A	G	G	Y
	16362	T-C		T	C	C	Y
12S rRNA	750	A-G	A/A/A/-	A	G	G	Y
	1041	A-G	A/T/T/T	A	G	G	Y
	1438	A-G	A/A/A/G	A	G	G	Y
16S rRNA	2706	A-G	A/G/A/A	A	G	G	Y
ND1	3394	T-C (Tyr30His)	Y/Y/Y/Y	T	C	C	Y
	4216	T-C (Tyr304His)	Y/H/H/H	T	C		Y
ND2	4491	G-A (Val8Ile)	V/I/I/V	G	A	A	Y
	4769	A-G		A	G	G	Y
CO1	7028	C-T		C	T	T	Y
	7142	T-C		T	C		Y
CO2	7861	T-C		T	C		Y
ATP6	8701	A-G (Thr59Ala)	T/S/L/Q	A	G	G	Y
	8728	TG-T (Trp68Gly)	W/W/W/W	TG		T	N
	8860	A-G (Thr112Ala)	T/A/A/T	A	G	G	Y
	9136	A-G (Ile204Val)	I/F/F/I	A		G	N
CO3	9242	A-G		A	G		Y
	9540	T-C		T	C	C	Y
ND3	10398	A-G (Thr114Ala)	T/T/T/A	A	G	G	Y
	10400	C-T		C	T	T	Y
ND4	10873	T-C		T	C	C	Y
	11719	G-A		G	A	A	Y
ND5	12705	C-T		C	T	T	Y
ND6	14308	T-C		T	C	C	Y
	14417	A-G (Val86Ala)	V/K/W/S	A	G		Y
CYTB	14766	C-T (Thr7Ile)	T/S/T/S	C	T	T	Y
	14783	T-C		T	C	C	Y
	15043	G-A		G	A	A	Y
	15301	G-A		G	A	A	Y
	15326	A-G (Thr194Ala)	T/M/I/I	A	G	G	Y

[a]Conservation of amino acids for polypeptides or nucleotides for RNAs in human, bovine, mouse, and Xenopus laevis.
[b]Cambridge reference sequence (Andrews *et al*[14], 1999).
[c]See online mitochondrial genome databases http://www.mitomap.org and http://www.genpat.uu.se/mtDB/.
CRS: Cambridge reference sequence; H: Human; B: Bovine; M: Mouse; X: Xenopus laevis.



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Figure 2 Alignment of partial *ND1* polypeptides from different species. The arrow indicates the tyrosine at position 30 (Y30) at the N-terminus of the *ND1* polypeptide, corresponding to the T3394C mutation.

Although both families had typical clinical manifestations of major depressive disorder, there were differences in penetrance, age at onset, and severity. The penetrance of the two families was 8.3% and 14.3%, respectively. This relatively low penetrance of MDD in two Chinese families having the T3394C mutation and its presence in one out of 167 controls suggests that, similar to previous mutations[29,30], the T3394C mutation alone is inadequate to induce the clinical manifestation. Therefore, the T3394C mutation requires modifying variables, such as nuclear histories, additional external variables, and mitochondrial haplotypes for phenotypic expression. Particularly, it has been demonstrated that mitochondrial haplotypes alter the penetrance and expressivity of MDD linked with primary mtDNA mutations[31]. The mtDNA of pedigrees NB011 and NB054 correspond, respectively, to the Eastern Asian haplogroups M9a3 and M9a.

The homogenous mutation T3394C was found in MDD families with different genetic backgrounds. The minimal penetrance of MDD among families with this mutation suggests that the T3394C mutation is a molecular base for the pathogenesis of MDD, but the mutation alone is not sufficient to cause phenotypic expression of MDD. This suggests that other mediators played a synergistic role in the pathophysiology of these families. Furthermore, the whole mitochondrial genome of the two families did not carry other highly conserved and functional mutation sites, indicating that polymorphic sites related to mitochondrial haplomorphism may not have a significant impact in the pathophysiology of two MDD families with the T3394C mutation. Moreover, mtDNA epigenetics may be involved in the occurrence of MDD, but research on the role of mtDNA epigenetics in diseases and therapeutic targets is insufficient. Therefore, nuclear-modified genes or external variables have a function in the phenotypic expression of MDD related T3394C mutations in these Chinese individuals. In conclusion, the *ND1* T3394C mutation may be a mitochondrial gene mutation site associated with MDD.

CONCLUSION

This observation of the T3394C mutation in two genetically unrelated individuals who suffer from depression strongly indicates that the current mutation might contribute to developing MDD. However, in these two Chinese families having the T3394C mutation, no functional mtDNA mutation was found. Therefore, the phenotypic manifestation of T3394C mutations linked to MDD may be affected by nuclear changed genes or environmental factors.

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FOOTNOTES

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EXPERT CONSENSUS

Identification and treatment of individuals with attention-deficit/hyperactivity disorder and substance use disorder: An expert consensus statement

Susan Young, Cyrus Abbasian, Zainab Al-Attar, Polly Branney, Bill Colley, Samuele Cortese, Sally Cubbin, Quinton Deeley, Gisli Hannes Gudjonsson, Peter Hill, Jack Hollingdale, Steve Jenden, Joe Johnson, Deborah Judge, Alexandra Lewis, Peter Mason, Raja Mukherjee, David Nutt, Jane Roberts, Fiona Robinson, Emma Woodhouse, Kelly Cocallis

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) often co-occurs with substance use (SU) and/or substance use disorder (SUD). Individuals with concurrent ADHD and SU/SUD can have complex presentations that may complicate diagnosis and treatment. This can be further complicated by the context in which services are delivered. Also, when working with young people and adults with co-existing ADHD and SU/SUD, there is uncertainty among healthcare practitioners on how best to meet their needs. In February 2022, the United Kingdom ADHD Partnership hosted a meeting attended by multidisciplinary experts to address these issues. Following presentations providing attendees with an overview of the literature, group discussions were held synthesizing research evidence and clinical experience. Topics included: (1) A review of substances and reasons for use/misuse; (2) identification, assessment and treatment of illicit SU/SUD in young people and adults with ADHD presenting in community services; and (3) identification, assessment and treatment of ADHD in adults presenting in SU/SUD community and inpatient services. Discussions highlighted inter-service barriers and fragmentation of care. It was concluded that a multimodal and multi-agency approach is needed. The consensus group generated a table of practice recommendations providing guidance on: identification and assessment; pharmacological and psychological treatment; and multi-agency interventions.

Key Words: Attention-deficit/hyperactivity disorder; Substance use; Pharmacokinetics; Assessment; Treatment; Comorbidity

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Core Tip: Attention-deficit/hyperactivity disorder (ADHD) often co-occurs with substance use (SU) and/or substance use disorder (SUD). The co-occurrence of ADHD and SU/SUD is associated with earlier onset and faster transition to more serious SUD, and reduced treatment effectiveness. This manuscript is the product of a consensus meeting of experts from ADHD and/or SUD services, across a range of clinical, academic, educational, occupational, and service-user sectors. A consensus was reached offering practical guidance to support practitioners working with young people and adults with ADHD and SU/SUD with recommendations for identification and assessment, pharmacological treatment, psychological treatment, and multi-agency interventions.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate levels of inattention and/or hyperactivity and impulsivity that interfere with functioning across multiple life domains (*e.g.*, personal, academic, work, family, social)[1,2]. Previously only considered a childhood disorder, the persistence of ADHD symptoms into adulthood is now recognised[3,4]. Meta-analyses estimate the prevalence of ADHD to fall between 5% and 7% in children and adolescents[5,6], and between 2.5% and 5% in adults[7,8].

Alongside physical comorbidities[9-11] psychiatric comorbidity is common in the ADHD population [12,13], with 75% reporting to have at least one other diagnosis[14]. One of the most common and impairing comorbidities is substance use disorder (SUD)[15-17]. Meta-analyses have shown that childhood ADHD is significantly associated with later substance use (SU) and SUD during adolescence and young adulthood[18,19]. ADHD is also highly prevalent among individuals with SUD[20-22]; a meta-analysis revealed around 23% of treatment-seeking individuals with SUD met DSM criteria for comorbid ADHD[23]. Accurately identifying ADHD in SUD contexts may be difficult due to high drop-out rates between screening and diagnostic assessments and/or possible unreliable historical information. This is further complicated by presenting symptoms that may be common to both ADHD and SUD, such as inattention, impulsivity and executive dysfunction[24,25].

Hence, the presentation of individuals with comorbid ADHD and SUD is complex. This may complicate identification and treatment[12]. Individuals with a dual diagnosis show more chronic patterns of SU, including earlier onset of SU and a more rapid transition to serious SU[26-28]. They are more likely to engage in polysubstance use[4,29] and experience greater difficulty remaining abstinent [30]. They demonstrate severe functional impairments across several life domains. These include increased risk of depression and suicide attempts[21], reduced quality of life[31], greater psychiatric comorbidity[32], accidents and crime[33,34]. When accompanied by comorbid oppositional defiant disorder (ODD) and conduct disorder (CD), there is an increased risk of premature death[35]. Research indicates poor treatment outcomes[36], with severity of SUD being a predictive factor for treatment outcome[37,38]. In those with a dual diagnosis, pharmacotherapy is less effective for treatment of ADHD when using standard dose, necessitating higher doses of medication[39].

Within the literature, the benefits of treating ADHD and comorbid SUD have been investigated, albeit with mixed findings. A meta-analysis of observational studies published in 2003 showed a significant reduction in risk of SUD in youths treated with stimulants compared with those who did not receive stimulants[40]. More recent observational studies have demonstrated a similar protective effect on later development of SUD[41,42]. Other studies, however, found comparable outcomes between children with and without medication treatment history[43].

Methodological issues with observational studies result in uncertainty regarding conclusions drawn as there may be baseline differences across groups. A meta-analysis of within-individual design studies, which are less prone to bias (although they cannot control totally for temporal effect), demonstrated a reduction of severity of SUD during periods when individuals were receiving medication, compared to periods when they did not[44].

A recent analysis of randomized controlled trials (RCTs) found a range of beneficial effects in the stimulant arm compared with placebo, including reduction of SU, increased abstinence, reduced craving, reduced frequency of ADHD symptoms, improved management of withdrawal symptoms, and decrease in the severity of ADHD symptoms[45]. This contrasts with a previous meta-analysis of 13 RCTs evaluating the effect of ADHD medication on outcomes in individuals with dual diagnosis which found a small to moderate reduction of ADHD symptoms but no beneficial effect for SU, drug abstinence or treatment discontinuation[39]. Carpentier and Levin[46] proffered some possible explanations for negative findings in their systematic review. These included high prevalence of polydrug use, presence of psychiatric comorbidity (additional to ADHD and SUD), possibility of suboptimal dosing of stimulant medication, generally low treatment retention, and influence of concurrent treatment (primarily cognitive behavioral therapy; CBT)[47].

There is increasing recognition of the need to identify and treat inappropriate use of substances by individuals with ADHD; and equally to identify and treat comorbid ADHD among those with SU or SUD. It is understood that treatment for those with concurrent ADHD and SUD may be complicated by the context in which services are being delivered. In the United Kingdom (as for many countries) individuals with ADHD are rarely able to access effective psychological treatments for their SU unless

this is associated with a level of impairment considered to be a 'disorder'[48]. Many young people do not fit within this criterion. Unfortunately, many healthcare practitioners do not feel they have the knowledge and skills to prevent this escalation, as intervention is commonly limited to specialist SUD services. Equally, expertise in treating ADHD within SUD services is rare. Uncertainty among practitioners on how to meet the needs for this complex group motivated the United Kingdom ADHD Partnership (UKAP) to convene a meeting attended by multidisciplinary experts to consider the complexities and challenges of working with young people and adults with concurrent ADHD and SU/SUD with the aim of providing helpful guidance and recommendations.

METHOD

Specialists in the fields of ADHD and SUD convened in London (United Kingdom) on 4th February 2022 for a meeting hosted by the UKAP. Meeting attendees included experts from ADHD and/or SUD services across a range of disciplines. Thirteen participants had medical qualifications/appointments, five had psychological qualifications/appointments and nine had academic qualifications/appointments. There was also representation by a service-user and an educational/occupational specialist.

The consensus group incorporated evidence from a broad range of sources. However, this largely reflects clinical practice and legislature in the United Kingdom, which may differ in other countries.

The meeting commenced with detailed presentations, providing an overview of the literature regarding the relationship between ADHD and SU/SUD. Following this, attendees separated into three breakout groups. Each group was tasked with providing a framework of guidance relevant to their assigned topic. Discussions were facilitated by a nominated group member and summarized by note-takers. Group participants drew on their clinical experience and research evidence, with discussions covering the following overarching topics: (1) Substances and reasons for use; (2) Identification, assessment, and treatment of illicit SU/SUD in young people and adults with ADHD presenting in community services; and (3) Identification, assessment, and treatment of ADHD in adults presenting in SU/SUD community and inpatient services.

Presentations and debate amongst attendees were audio-recorded and transcribed. A note-taker was allocated to each breakout group and following the meeting these notes were circulated to breakout group participants for review and approval. At the end of the meeting breakout groups presented respective conclusions and recommendations for debate, discussion, and approval by all attendees. All materials (transcriptions, electronic slide presentations and breakout group notes) were synthesized by the medical writer (KC) into a draft manuscript. Further drafts were produced by the lead author (SY) working in collaboration with the medical writer (and with consultation with some authors where necessary). A draft was then circulated to all authors for review and revisions; this did not generate any disagreements between authors. Following further revisions, a final draft was circulated to all authors for agreement and approval.

The consensus is based on published research, but it also reflects the views of the authors based on their practical experience. Acknowledging that children, adolescents, adults, and older adults experience different challenges and treatment demands[49,50], the consensus group considered differences in biopsychosocial needs across age groups.

RESULTS AND CONSENSUS OUTCOME

Substances and reasons for their use by people with ADHD

Alcohol and nicotine are the most commonly used recreational substances used among adolescents and adults with ADHD but cannabis is the most used illicit substance[18,19,38,51,52]. Stimulants such as cocaine, amphetamines and methamphetamine (Ice) are also common[53,54]; a meta-analysis reported the prevalence of cocaine use in adults with ADHD to be around 26%. Ten percent had cocaine use disorder[55].

Various reasons have been proposed for SU among individuals with ADHD. Individuals with ADHD often claim that, prior to their diagnosis, they used substances as a form of self-medication to attenuate ADHD symptoms and associated impairments. However, there is no robust empirical evidence to support this proposal[56,57]. Individuals report using substances frequently to help them to sleep, manage fluctuations in mood, and improve attention and executive functioning[58-60]. It has also been posited that individuals with ADHD may be more susceptible to using substances due to impulsivity (behavioral inhibition hypothesis)[61]. This, together with immediate gratification and reward-seeking behaviour may collectively impact on the positive and negative reinforcement of substances and their potency.

Adolescents and adults with ADHD have high rates of comorbidity with other conditions, many of which are associated with increased risk of SU. CD and ODD may explain the association[62-64]. Other

studies have shown that depression, bipolar disorder, and antisocial personality disorder all convey an elevated risk for SU/SUD among individuals with ADHD[32,62,65-68]. Other potential reasons include increased exposure to psychosocial risk factors (*e.g.*, parental SU/SUD, peer pressure, predatory grooming and exploitation, financial, family and work-related stressors, chronic low self-esteem, feelings of demoralization and failure, trauma and fear responses)[14,59].

Table 1 shows key aspects of the pharmacology of several commonly used recreational drugs that might be used by people with ADHD. The primary molecular targets and neurotransmitters that are impacted by interactions of different drugs are shown, most of these are not dopamine.

Biological factors such as speed of brain entry of stimulants may influence which substances are used [69]. Figure 1 shows three examples of drugs with accelerated brain entry.

The consensus group agreed that there is a complex interplay between an array of factors, which results in individuals with ADHD initiating use of illicit substances. Across the lifespan, motivation for using these substances may transition across several phases towards dependency[48,70,71].

Identification, assessment, and treatment of illicit SU/SUD in young people and adults with ADHD presenting in community services

When to refer individuals with ADHD for support for their SU/SUD: There was extensive debate regarding what would be considered a 'red flag' indicative of a SU problem developing in young people and adults with ADHD. Experimental drug use is common, with the highest level of experimental use usually occurring during adolescence. This in itself may not necessarily be a cause for concern. The threshold for what may be considered concerning or problematic is likely to vary; a person, parents, family members, teachers and employers may all have differing perspectives. It was agreed that 'red flags' should be understood in relation to the person's community, social, economic, religious, and cultural circumstances. This includes contexts where SU may be normalized within the immediate environment the person inhabits. The boundary between use and misuse is likely to be influenced by what is normative within the individual's immediate social network (family, peer group and wider neighborhood). It may also be influenced by politics and sociocultural values.

When considering 'red flags' (indicating possible SU/SUD), one should focus on any changes in presentation that are out of character for the person. Typically, this is a decline in self-care, physical and/or mental health, and daily functioning, often associated with social and occupational problems. Table 2 details several markers that may prompt concern; however, these are also markers of other evolving mental health and/or social problems. Thus it is the clustering of multiple markers together across various life domains that is informative. The key message is to ensure that SU/SUD is not disregarded as a potential explanatory factor for change in presentation.

The decision to refer to addiction services should be determined by level of impairment and distress and the wishes of the individual (and parents/caregivers/partner), if appropriate. It was noted that the legal class of substance (*e.g.*, Class A drugs which are most likely to result in the most serious harm, compared with Class B and C drugs) and method of use (*e.g.*, injecting) may determine the level of concern and/or the level of impairment due to associated harm to user.

The way in which the referral is made may depend on how the concern has developed; whether the individual has disclosed their use and/or expressed concerns, or whether it has been uncovered by other means (*e.g.*, found on them/urine testing), and whether there are attempts to deny use. The consensus group agreed that it is important to spend time building rapport with the individual and to develop a shared understanding of SU and how it fits in within a broader context.

Referral pathways are different across regions dependent on commissioning and funding. Anecdotal accounts from the consensus group emphasized reduction/closure of young people's addiction services, resulting in young people being 'bounced around' between different services in order to find appropriate support. Some consensus group members reported that some child and adolescent mental health services and adult services do not accept referrals for individuals with SU difficulties. Exclusion criteria may differ according to type of substance and methods used. Later in adolescence, young people may be referred early to adult addiction services, depending on region.

The consensus group agreed that ADHD services should have an agreed procedure for dealing with concurrent SU/SUD, taking into consideration regional available resources (health, social and third sector).

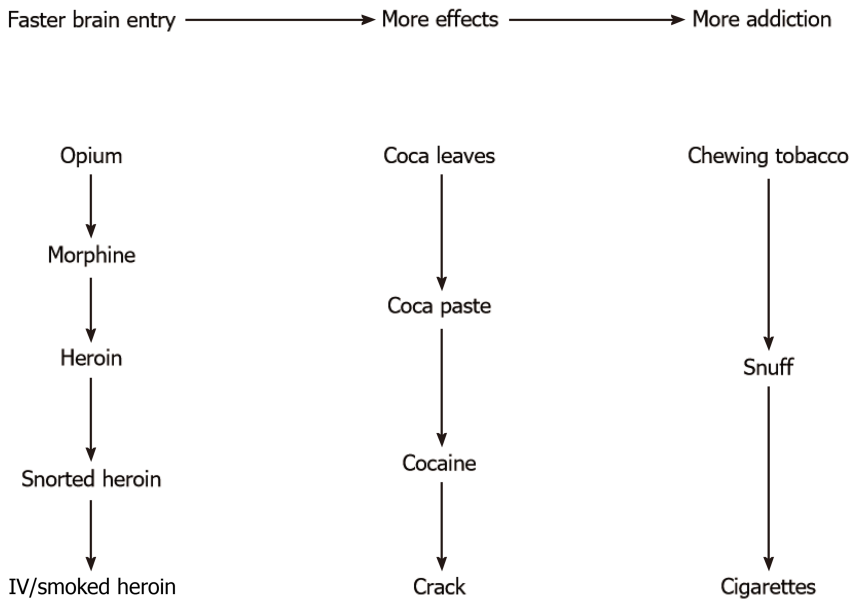
Assessing people with undiagnosed ADHD: Assessment of ADHD and SU/SUD can be challenging, particularly when ADHD has not previously been diagnosed. Like other diagnoses, the diagnosis of ADHD, with or without SU/SUD requires careful and comprehensive clinical assessment. This should include a full developmental history, mental health history and current mental state examination, medical history, educational/employment history, social history, and, when helpful, assessment of cognitive executive functioning difficulties. It is also important to consider family history of ADHD and SU/SUD, and other psychiatric and neurological problems. Gender differences in presentation should be considered (*e.g.*, symptom severity for hyperactive-impulse symptoms may be lower in females) which may result in missed diagnosis or misdiagnosis[72].

Table 1 Pharmacology of commonly used recreational drugs that might be used by people with attention-deficit/hyperactivity disorder

Drug type	Primary target	Main effects/transmitters	Other actions	Antagonists/blockers
Opiates	Mu opiate receptors		Kappa and delta opiate receptors	Naltrexone Naloxone Nalmefene
Stimulants				
Cocaine	DAT	Inc. Dopamine	Local anesthetic Inc. 5HT	[BP-897 partial agonist]
Amphetamines	DAT	Inc. Dopamine		Mecamylamine
Nicotine	Nicotinic ACH receptor	Inc. Dopamine		Varenicline
Sedatives				
Ethanol	GABA/glut	Inc. GABA	[1]Inc. Dopamine	No
Benzos	GABA	Dec. glutamate		Flumazenil
GHB	GABA	Inc. GABA		No
Solvents	N/A			No
Cannabis	CB1 receptors	[1]Dopamine		Rimonabant
Ecstasy	5HT transporter	Inc. 5HT	Some DA release	[1]SSRIs
LSD	5HT 2 receptors	Stimulate 5HT		5HT2 receptor antagonists

[1]Postulated but not proven.

Column 2 lists the primary molecular targets for the different pharmacological classes of drugs. Column 3 lists the neurotransmitters that are impacted by the interactions listed in column 2. Column 4 lists other molecular targets that these drugs can influence. Column 5 lists antagonists or blockers that can be used to stop or reverse the effects of the drugs. DAT: Dopamine transporter; GABA: Gamma-amino-butyric acid; inc: Increased; dec: decreased.



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Figure 1 Examples of drug modification to accelerate brain entry. Brain entry escalates with the downward direction of the arrows.

Assessment of ADHD with comorbid SU/SUD involves careful examination of symptom severity and frequency, chronicity, pervasiveness, degree of impairment across life domains, and childhood onset. A useful tool to assess impairment may be the Weiss Functional Impairment Rating Scale[73]. Nevertheless, while rating scales are useful aids for clinical assessment, the consensus group emphasized the importance of services not rigidly adhering to thresholds and cut-offs as this may lead to high proportions of false positives and negatives.

Table 2 Markers of potential concern for substance use/substance use disorder

Life domain	Markers
Physical	Declining physical health including nausea and abdominal pain
	Looks fatigued
	Disheveled
	Unexplained weight loss
	Dilated pupils, redness in eyes
	Muscle in-coordination
	Poor personal hygiene
	Sniffing
	Administration scars (needle entry marks)
Daily functioning	Unaccountable increase in expenditure
	Difficulty managing daily living tasks (including budgeting, staying on top of household tasks)
	Poor punctuality
	Possession of substances, hiding substances
	Accessing of prescription drugs in the home
	Difficulty managing underlying health conditions (*e.g.*, epilepsy, diabetes)
Home life	Absconding from home (adolescents)
	Receiving packages in the post which they are eager to intercept
	Driving offences
	Accidental injuries, including road traffic accidents
	Increased risk of injury and assault (both to self and others)
	Difficulties fulfilling chores and/or parenting responsibilities
	Social services involvement
	Debts
	Gambling
	Housing problems and homelessness
Educationand work	Truancy/absence from school/college or work
	Deterioration in academic/work performance
	School detention, suspension, expulsion
	High turnover of short-term employment
	Official warnings and disciplinary procedures at work
Social	Social withdrawal
	Social exclusion
	Marginalized
	Sudden change in social groupings
	Part of a 'bad crowd' (gangs, friends much older than peers)
	Friendship and intimate relationship problems
	Domestic violence
Mental health	Apparent deterioration in mental state and health
	Signs of emotional or physical withdrawal from others
	Paranoia
	'Unexplained' onset and/or change of mood swings

	Presenting as exhilarated or with excessive confidence
	Low mood and depression
	Irritability, agitation
	Anxiety
	Paranoia
	Confusion, delusions and/or hallucinations
	Emotional lability
	A&E admissions due to mental health condition
Behaviour	Early use of experimentation with drugs including early onset vaping/smoking (*e.g.*, under 12 yr)
	Excessive use of energy drinks
	'Unexplained' onset of behaviour that seems 'out of character'
	Change in personality/demeanor
	Lack of constructive interests and activities
	Disengagement of 'healthy' leisure activities (change in interest)
	Increased energy, restlessness and disinhibition
	Conduct problems and/or oppositional behaviour
	Irritable, agitated, aggressive and/or violent behaviour
	Risk taking behaviour (shoplifting, theft from home and/or others)
	Risky/compulsive sexual behaviour (promiscuity, risk of pregnancy, sexually transmitted infections)
	Solitary drug use
	Missing appointments
	Parenting issues leading to safeguarding concerns
	Self-harming behaviors
Speech and cognition	Changes in cognitive functioning at different times of the day
	Difficulty sustaining concentration
	Increased alertness
	Confusion
	Memory problems and loss
	Change in usual speech presentation (*e.g.*, slurred, rapid or rambling speech)
	Reference to 'needing' substances (*e.g.*, to help sleep, improve confidence) rather than use for fun or enjoyment
	Unexplained improvements in functioning

It is essential to determine if ADHD or SU/SUD, or both can best explain the presenting symptoms. One key consideration is whether ADHD is masked by SU/SUD. Some individuals report that substances have a countering effect on their ADHD symptoms (*e.g.*, the consensus group shared anecdotal accounts of experiencing patients who report stimulant use has a calming effect rather than an elating effect). Examining the temporal course of ADHD-like symptoms and SU/SUD is crucial. Assessment must be conducted by qualified healthcare professionals with training and expertise in assessing dual disorders so that differential diagnosis can be considered[22]. It is not advisable to conduct an assessment when an individual is under the influence of substances at the time of the assessment and/or when at a stage of withdrawal[24].

Assessing people with diagnosed ADHD: Individuals who already have a primary diagnosis of ADHD should be carefully monitored for SU. This might include alcohol, tobacco, caffeine, study drugs (*i.e.*, accessing prescription stimulants to help focus and/or stay awake). It is important to obtain information regarding the age of initiation for each substance, frequency of use, methods of administration, the social context in which use takes place, the effects of the substance on the person's cognitive, psychological, physiological, and behavioral functioning, the medical, educational/employment, social and medical problems attributable to SU, and any previous treatment. An association between problematic video gaming and nicotine, alcohol and cannabis use has been reported, so asking about these factors

(and internet use more broadly) may be helpful[74].

When conducting the assessment with young people, it is important to consider the role of parents/caregivers (and taking account of the wishes and needs of the young person). There may be additional physical, criminogenic, and safeguarding risks associated with SU which will need to be addressed. Like other assessments, the person should be informed of the confidentiality of information shared and circumstances in which this will be breached.

The utility of SU/SUD screening assessments as an indicator for further assessment was discussed. A commonly used screening tool recommended by the consensus group for young people is CRAFFT. This is an acronym generated from six core questions relating to the experience of young people: (1) Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs? (2) Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in? (3) Do you ever use alcohol/drugs while you are by yourself, ALONE? (4) Do you ever FORGET things you did while using alcohol or drugs? (5) Do your family or FRIENDS ever tell you that you should cut down on your drinking or drug use? and (6) Have you gotten into TROUBLE while you were using alcohol or drugs?[75].

The authors suggest that young people who complete the CRAFFT before seeing their healthcare practitioner are more likely to answer honestly[76]. Completed self-administered copies can then be used by practitioners to guide discussions about SU.

For adults, commonly used screening tools include the Drug Use Disorders Identification Test[77], Drug Abuse Screening Tool (DAST)[78] and Alcohol Use Disorders Identification Test (AUDIT)[79]. The DAST and AUDIT have demonstrated acceptable reliability and validity among adults seeking ADHD clinical evaluation[80].

For young people and adults alike, it is important to identify the substances the person is using, and to discern the intended (*i.e.*, function) and unintended consequences of use. This may differ for different substances. This can be explored in relation to the five-stage pathway (experimental, social, instrumental, habitual, dependent) (refer to Young and Bramham[81] and/or Young and Woodhouse[48] for more information). Individuals should be encouraged to acknowledge the adverse consequences of their SU across physical health, mental health, personal functioning, risky behaviour, interpersonal relationships, ability to study or work, and contact with criminal justice system (CJS).

However, many people with ADHD have difficulty engaging in consequential thinking processes, requiring them to be empathically guided through the process. It can be helpful to start by first acknowledging the benefits of SU before considering disadvantages.

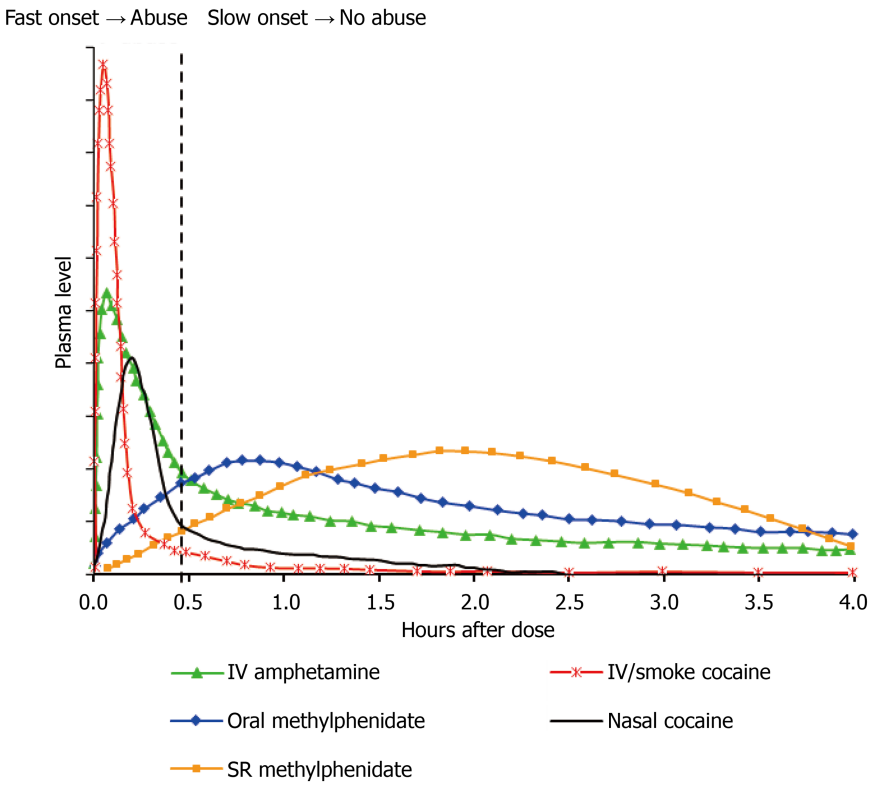
Understanding how SU and ADHD have interacted in the past and present can help services and the individual to understand internal and contextual motivational mechanisms which increase or attenuate risk of SU. This will be helpful in identifying treatment areas. One assessment method involves a functional analysis of behaviour which systematically assesses the antecedents and consequences of specific behaviors. For SU associated behaviors, this involves the assessment of internal and external factors that trigger SU, including factors of positive reinforcement (*e.g.*, euphoria) and negative reinforcement (*e.g.*, numbing of feelings). In turn, the analysis is a helpful strategy for identifying targets for intervention.

Generating chronological timelines can be a helpful technique to record and identify potential interactions between important aspects of ADHD symptomatology (*e.g.*, periods of heightened/lower symptoms, periods of deterioration/functional improvement) and SU (*e.g.*, onset, drug free periods, escalation of use, serious difficulties including episodes of drug-induced psychosis). Mapping these out in this way can be helpful to discern associations concerning onset and maintenance of use, triggers of risk and optimal management.

Pharmacological treatments

Historically there have been concerns regarding prescribed stimulant medications' abuse potential, addictive nature, or that they may worsen pre-existing SU/SUD. These concerns are unfounded[43,82-86]; the formulations that are used are not addictive. Tolerance effects are not clear. Some clinicians have noted a reduced benefit from stimulants over time in some patients, although this is not a universal problem. Neuroimaging studies (*e.g.*, PET studies[87]) point to an increase in dopamine reuptake receptors in adults with ADHD treated for up to 12 months with stimulants. This evidence suggest that tolerance may happen during treatment with psychostimulants. However, the experience of consensus group members was that individuals are more likely to be poorly compliant with stimulant medication or choose to stop taking it, rather than seek higher doses.

Nevertheless, for individuals with comorbid SU/SUD, long-acting preparations are recommended rather than immediate release due to their lower abuse potential (immediate release stimulants are more likely to be crushed to a powder and snorted or used intravenously)[88]. The time course of common stimulants taken *via* different routes is shown in Figure 2. Speed of plasma peaks determines abuse ability. The intra-venous route produces the fastest brain entry and highest peak concentration with intra-nasal cocaine somewhat behind. These effects explain the high propensity for liking and hence abuse of these. Oral methylphenidate peaks at about one hour and slow-release forms even later; a similar profile is seen for lisdexamfetamine. In general, drugs with a low peak concentration and where



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Figure 2 Speed of plasma peaks for different types of stimulants. IV: Intravenous; SR: Slow release.

the peak occurs after 30 minutes shows low abuse liability. Notably, lisdexamfetamine is a pro-drug (rather than a slow-release preparation) that has to be metabolized in the blood to release the active ingredient (dexamfetamine). This metabolic step explains why even after intra-venous injection lisdexamfetamine does not produce a noticeable 'high' hence providing a low abuse liability[69].

The consensus group emphasized that pharmacological treatment nihilism is not appropriate. It is essential that individuals with ADHD and SU/SUD are not deprived of effective medications. However, short-acting preparations should be reserved for a very circumscribed group (*e.g.*, in contexts where there is possibility for supervised consumption).

Medication should be informed not only by the effectiveness of the medication but also by safety and tolerability (*i.e.*, to physical and mental health).

There was agreement that non-stimulant medicines should generally be reserved as a second line treatment option (even in dual diagnosis cases) as research has shown that, on average (*i.e.*, at the group level) they are less effective than stimulants[89] raising risks of non-compliance. Compared with stimulant medications, where the benefits can be very quick (sometimes within a few days), non-stimulant medications take several weeks to have a therapeutic effect[53]. An exception to this, may be for those misusing alcohol; atomoxetine may reduce alcohol cravings[90].

There was debate about whether voluntary drug testing should be used to monitor use of substances. Drug testing is generally used to monitor compliance with drug rehabilitation programs where there may be suspicions of non-adherence. The overarching view was that where clinicians have concerns about severity of SU, support from specialist SUD services should be sought.

Research has shown that heart rate and/or blood pressure increases in individuals with ADHD treated with stimulants[91,92]. Small but persistent increases in heart rate and/or blood pressure over a sustained period has raised concerns. Meta-analyses however have found no significant link between ADHD medication and serious cardiovascular outcomes such as sudden death, stroke, or myocardial infarction[93,94], though this evidence reports at a group-level, so it is not informative at an individual level. Where there are concerns regarding cardiovascular risk, a cardiologist should be consulted. This is considered particularly important when there is a personal or family history of cardiovascular conditions (*e.g.*, premature sudden/unexpected death in children or young adults, clinically important arrhythmias, prolonged QT syndrome, hypertrophic cardiomyopathy, and Marfan syndrome). For safety[95], the group stressed that heart rate and blood pressure should be measured before initiating medications and routinely during treatment, and titration should be slow. It is also worth being aware that people with ADHD may be more sensitive to the effects of or dependence on sedatives such as alcohol.

Treatment with ADHD medication, especially stimulants, may increase the health risks from the concurrent use of recreational drugs[96]. These are presented in Table 3. In general, there are few specific hazards from the interactions of ADHD medication with recreational drugs with the exception of other powerful stimulants (especially cocaine/crack) which add to the burden on dopamine and noradrenaline neurotransmitter effects and the potential for cardiac events and seizures[96].

Considering when to commence ADHD medication was an area of intense debate. Consensus participants acknowledged that ADHD symptoms and associated impairments make it more difficult to treat SU difficulties, and vice versa. The consensus group agreed that ideally SU would be stabilized (*e.g.*, by the individual demonstrating a level of improved functioning with life not being primarily organized around substances) before initiating medication for ADHD. When this is not possible, services may need to be pragmatic, with decisions informed by an individual risk assessment. There was agreement that abstinence is not necessary for individuals to benefit from ADHD medication.

In the United Kingdom there are lengthy waiting lists for an assessment of ADHD (some being two years and over)[97]. Hence individuals may have stabilized SU at point of referral but relapse whilst waiting. It was agreed that there may be a role for prioritization of those with SUD within ADHD services. This is done for other groups across other health services (*e.g.*, pregnant women, veterans, those with long-term conditions).

Prescribing issues for certain groups were highlighted in discussions. Evidence indicates that adherence to medication declines in teenage years. This has been attributed to adverse effects, sub-optimal response, reduction in parent supervision, increased need for autonomy, comorbid conditions, and social stigma associated with ADHD diagnosis and taking medication[98]. The consensus group noted that this may be of particular concern, acknowledging that young people may be vulnerable at this time to misuse substances to manage their symptoms[61]. Research suggests that treatment with ADHD medication may protect against SU/SUD, but only if the medication is taken continuously[40,86,99,100].

It is imperative to provide psychoeducation to encourage young people to understand and take ownership of their treatment[101]. Provision of developmentally appropriate healthcare within services may also be of benefit[102], a summary of which is provided in Table 4[103].

The consensus group acknowledged the complexity of prescribing and monitoring medication among adults. As individuals get older, they are likely to be prescribed other medications to treat comorbid mental health and physical health conditions. Practitioners should refer to summaries of product characteristics when considering prescribing needs and potential interactions with other medications. Cardiac risk increases with increasing age, which should be considered when prescribing. Monitoring of weight may also be appropriate for adults who are misusing substances, as aside from the potential of stimulant related suppression of appetite, they may prioritize buying drugs over food.

ADHD is associated with working in unskilled occupations (*i.e.*, those not requiring formal education)[104]. Anecdotal accounts from consensus group members discussed individuals working in unskilled occupations with varying shift patterns who use substances chronically. This disrupts sleep patterns and makes monitoring and review of pharmacological treatment problematic, for example, setting specific times-a-day prescriptions, and difficulties attending clinic appointments, especially if they need to attend multiple services (ADHD and SUD).

Psychological interventions

Multi-modal treatments are emphasized for young people and adults with comorbid ADHD and SU/SUD[105]. Several RCTs investigating pharmacological interventions for individuals with co-occurring ADHD and SU/SUD have demonstrated few group differences between medication and placebo group. These studies have had adjunct psychological therapies such as CBT or motivational interviewing (MI), leading to some authors positing that observed improvements may be attributed to the psychological therapy. The design of these studies prevents firm conclusions being drawn, although suggests that psychological therapy is a useful intervention for treating SU/SUD among those with ADHD[59].

Psychological approaches vary across the lifespan and the content of the treatment should be tailored to meet individual need[81]. Specific assessment and treatment techniques for young people and adults with ADHD and SU/SUD can be found in Young and Bramham and/or Young and Woodhouse[48,106]. The consensus group agreed that the following adjustments and psychological interventions will be helpful.

Adjustments to treatment: Executive functioning and memory deficits are commonly reported in individuals with ADHD[107,108]. In addition, chronic use of substances has been found to be associated with visuospatial and memory deficits[109]. Such difficulties can make engaging in therapy and sticking to long-term goals challenging[110]. It is important to accommodate for deficits associated with ADHD and/or SU/SUD. Where neuropsychological testing has been conducted, the strengths and weaknesses profile can be used to inform adaptations to the treatment process. Some specific adjustments to traditional treatment approaches that should be considered include: using text and/or email reminders to reduce non-attendance due to forgetfulness, adapting language and behaviour (implicit rather than explicit conversational approach), adjusting the pace of introducing new elements in treatment, making the treatment more concrete, using material that is easy to understand, greater use of supplementary

Table 3 Potential increased risks from use of recreational drugs in people treated with attention-deficit/hyperactivity disorder medication

Substance	Risks	Risk level	Antidotes
Alcohol	Intoxication, dependence	++	
Cannabis (d9THC)	Anxiety, paranoia	+	Benzodiazepines
Cocaine	Cardiac problems, seizures	+++	b-blockers – benzodiazepines
LSD/psychedelics	Paranoia	+	Risperidone/olanzapine
Ketamine	Dependence, bladder damage	++	
MDMA	Cardiac problems	++	b-blockers
Methamphetamine	Dependence, paranoia	++	Risperidone/olanzapine
Nitrous oxide	Intoxication, neuropathy	+	Vitamin B12
Opioids	Respiratory depression, dependence	++	Naloxone naltrexone
Sedatives	Intoxication, ataxia	+	Flumazenil (for benzos)
Spice/synthetic cannabinoids	Cardiac problems, seizures	+++	Rimonabant

+: Moderate risk; ++: Considerable risk; +++: High risk; LSD: Lysergic acid diethylamide; MDMA: Methylenedioxymethamphetamine.

visual materials, repetition and consolidation of core concepts, a high level of structure, shorter and/or more frequent sessions, mid-session breaks, and identify support between sessions for homework tasks.

It is recommended that individuals are provided with a notebook which they should be encouraged to bring to sessions. This serves as a record of the treatment, including the strategies and techniques they have found most helpful and later becomes a resource when treatment has ended. Any handouts summarizing key information should be secured in the notebook. Exercises should be completed in the person's own writing and their own words (with careful guidance from the practitioner, as needed) to facilitate 'ownership' of the problem, and in turn responsibility and action. For individuals who prefer to keep electronic records, handwritten notes can be scanned for storage on electronic devices.

MI: Motivation is an important predictor of treatment outcome[111]. However, motivation to stop misusing substances may be especially challenging when individuals perceive themselves to use them to self-medicate. MI is a client-centered method for enhancing motivation to change by exploring and resolving ambivalence[112] and it may be an effective model to work for adults with ADHD and coexisting SU/SUD[113]. MI techniques involve expressing empathy, supporting self-efficacy, rolling with resistance, and developing discrepancy. A central tenet of MI is to avoid confrontation as this is posited to incite resistance. Individuals who misuse substances go through several stages in a 'transtheoretical model of change' (precontemplation, contemplation, preparation, action, maintenance)[112,114]. MI is suggested to be particularly helpful in the initial motivational stages (precontemplation and contemplation)[48].

Different MI techniques can be used depending on what stage of the 'transtheoretical model of change' the person is in (*i.e.*, readiness to change). An individual's readiness to change is dependent on many factors (*e.g.*, environmental factors such as friends being drug users and/or living in an area where drugs are frequently offered, psychological factors such as beliefs that they are unable to function adequately without using substances), and thus it is important to consider a biopsychosocial perspective. Stages are cyclical (not linear), and it is common for individuals to oscillate between stages. Practitioners need to be aware of the persons current motivational stage and should monitor interest to engage in treatment, adapting treatment interventions as needed. Helpful tools to explore ambivalence and encourage change include use of dissonance charts and decisional balance sheets (please refer to Young and Bramham[106] for further details about these techniques). The group considered that it may be helpful for MI techniques to be employed more broadly by key frontline contacts within services, which may necessitate further training.

Formulation: Formulation (or case conceptualization), beyond diagnosis[115] is central to intervention planning. Within the formulation it is important to consider the bidirectional relationship between ADHD and SU/SUD. Formulation can help both the practitioner and individual make sense of the individual's experience in a flexible and systematic manner. One framework that may be useful is the Five Ps model[116,117]. This is an idiographic-based framework which enables systematic and holistic examination of multifaceted and complex subjects such as comorbid ADHD and SU/SUD. The Five Ps model organizes information into five sections: (1) Presenting problem; (2) predisposing factors; (3)

Table 4 Developmentally appropriate healthcare dimensions and examples of implementing them into practice

Dimensions of DAH	In practice
Biopsychosocial development and holistic care	Assess wider aspects of young person's life using approaches such as HEEADSSS tool (Home, Education, Eating, Activities, Drugs, Sexuality, Suicide, Safety)
	Consider stage young person is at in their development rather than chronological age
Acknowledgement of young people as a distinct group	Opportunity for young person to be seen independently (for some or all of the consultation)
	Flexible access to service (*e.g.*, outside school/college hours)
	Dedicated clinics and space (*e.g.*, age-banded clinics, appropriately sized seating, magazines/posters of relevance and interest)
	Consideration of different ways young person can contact the service (*e.g.*, digital technologies rather than letters/phone calls)
	Explain confidentiality and rights; display confidentiality policy in waiting room
Adjustment of care as the young person develops	Communication to be adjusted in line with cognitive development
	Appointment letters addressed directly to young person in addition to parents/caregivers, when needed; language used is clear
	Use of simple self-assessment tools which may feel less awkward for young person
	Record contact details for both young person and parents/caregivers
Empowerment of the young person by embedding health education and promotion	Psychoeducation provided to young person and parents/caregivers
	Shifting emphasis and supporting family to move from shared-care to self-management as the young person gets older
	Check out with young person how they would like parents/caregivers to be involved
	Involve parents/caregivers in treatment decisions in ways that have been agreed with young person
	Sign-posting young person to local services, as appropriate
	Discuss with young person their confidence and independence in making appointments, managing medication, *etc.*
Working across teams and organizations	Workforce training in developmentally appropriate healthcare, including strength-based approaches such as solution-focused and motivational interviewing
	Adult service included in transitioning planning prior to transfer (*e.g.*, multi-disciplinary team meetings with adult and child teams present, adult services copied into correspondence)
	Transition planning to start early (aged 13-14)
	Opportunity for young person to visit adult service prior to transfer; provide information leaflet about service to be transferred to
	Young people issues are considered in service policies and guidelines; consistency of policies in child and adult services
	Young people's participation at all levels of delivery

DAH: Developmentally appropriate healthcare.

precipitating factors; (4) perpetuating factors; and (5) protective factors.

Practitioners may find it helpful to rename these using more accessible language for individuals, particularly young people. This may be current (what is happening now?), past (what has happened in the past that may be important?), triggers (what sets things off? what was happening when difficulties started?), what keeps things stuck (things that keep difficulties going and/or make change difficult), and positives (positives in life, including own strengths and support from others). These Five Ps should include biological, cognitive, environmental/systemic and personality considerations and the relationships between factors should be explored.

Psychoeducation: Psychoeducation is an important part of treatment that facilitates treatment engagement. Psychoeducation may be provided more generally to family members, but it is important that key information is also directed to the young person in the absence of family members. This is because without 'buy-in' from the individual there is a risk they will just go through the motions to keep people happy or drop out of treatment. It also facilitates informed decision-making and may improve medication adherence and outcomes[118].

Psychoeducation should not be considered a one-off event but rather a process which should be returned to as needed. Psychoeducational interventions are particularly important at key points of service and/or personal transition, with differing topics covered specific to changing biopsychosocial needs and demands. For children and adolescents there may be misconceptions about medication. Discussions should include basic information about ADHD, the purpose and benefits of medication and the long-term consequences of SU. The latter should include legal consequences (*e.g.*, providing substances to a friend can result in supply charges, in turn affecting ability to apply to law or medical schools and travel to destinations such as the United States). For older adolescents and adults, psychoeducation should include discussion about driving including the increased risk of accidents, and legal penalties if convicted of driving under the influence of alcohol or drugs (*e.g.*, losing driving license, a fine, imprisonment, and a criminal record). Both accidents and convictions are likely to substantially increase insurance costs (in the United Kingdom convictions have increased since the introduction of roadside drug testing). Psychoeducation should also include information regarding misconceptions around medication increasing the likelihood of addiction, safety of medication when using substances (*e.g.*, increased risk when binging) and how with age risk significantly increases.

When approaching the care of young people with co-occurring ADHD and SU/SUD, engagement and support of families/carers is critical. Societal connotations about SU can be disparaging and group workshops are helpful in negating feelings of shame through sharing experiences in a supportive environment. Given the heritability for ADHD[108], some parents/caregivers are likely to also have ADHD (possibly unrecognized) and it is important the psychoeducational interventions are facilitated in a manner that aids understanding and engagement. Discussion topics may include the increased risk of SU/SUD for those with ADHD; potential signs and symptoms to be aware of; when and how to seek treatment; treatment options; value of adherence to ADHD medication; how to support a young person (dos and don'ts); refuting myths and misconceptions; dispelling stigma and feelings of shame; and coping skills for parents/caregivers.

CBT: The content of CBT interventions should be adapted to meet individual needs associated with cognitive and emotional functioning of individuals with ADHD and SU/SUD. Individuals with concurrent ADHD and SU/SUD may find it difficult to envisage the potential for change; their impulsivity, together with physiological and/or psychological SU dependency, may leave them perceiving they have little choice and/or will. Agreeing realistic goals is essential and should be based on the individual's presentation and needs (ADHD symptomatology, severity and complexity of SU/SUD, physical health, mental health, internal and external resources, social and cultural systems, and the person's motivation). To increase motivation, goal selection should be a collaborative effort and the goal concrete and relevant. When considering level of functioning (emotional, behavioral and cognitive), it is often necessary to help guide the person in 'fine tuning' treatment goals. Goals which are abstract and/or unrealistic are less likely to be achieved and in turn are likely to negatively affect motivation, confidence, and self-esteem, which may already be fragile[119,120]. Hence goal negotiation is a process and to do this effectively it is important that a good therapeutic alliance has been developed.

Individuals should be invited to use self-reinforcement techniques as useful reminders of their goals, which can help nudge them toward achieving them. These should have some personal meaning. Examples may include mobile phone screensaver with an important word or phrase or symbol, brightly colored sticker on the strap of a wristwatch or the back of a mobile phone, written message in the 'notes' app of a mobile phone, flashcards that are carried in a wallet. A reward system should also be incorporated to motivate new behaviour. Individuals with ADHD struggle to delay gratification; teaching individuals to give themselves rewards on a 'little and often' basis may help to satisfy immediate gratification need and reinforce new behaviour. One form of reward is encouraging 'self-talk' (*e.g.* by giving self-praise, encouraging and motivating statements). It may however be that individuals prefer more material/tangible rewards. Small rewards may be awarded for achieving small steps, with larger rewards introduced at the end of longer periods of sustained behaviour. The person should also be encouraged to share their success and progress with their support network (who will respond positively). This will help to maximize motivation and encouragement.

When working with young people, behavioral-oriented interventions may be more of a focus than cognitive interventions (due to the abstract nature of thinking required). It is important that individuals learn behavioral skills that can be applied on a long-term basis. This should encompass developing skills and confidence to manage potentially high-risk situations such as being offered substances and/or when there is peer pressure. One of the best methods of acquiring new behaviors is to practice in role-plays, where individuals can learn and practice strategies that involve problem-solving, planning, and impulse control. The aim is to learn specific skills that can be automatically applied, minimising cognitive load during real-life stressful situations. Overt rehearsal has been found to enhance treatment effects[106]. In-session practice is considered particularly important for individuals with a dual diagnosis of ADHD and SU/SUD as it is expected they may have difficulty completing practice exercises outside of session.

Individuals should be made aware of emotional and physical states that are likely to increase risk of SU, including when they are most likely to be sensitive to cravings, urges and withdrawal. Identifying and engaging in scheduled activities during 'risk periods' as part of a wider structured timetable can

help young people to maintain abstinence when they are likely to be at their most vulnerable. They should also be guided to use replacement techniques (*i.e.*, replacing substances with something that is less harmful) to assuage cravings and urges. Methadone is commonly prescribed as a replacement for heroin, and nicotine patches, gum, lozenges and vapes/electronic cigarettes as substitutes for cigarettes. Similarly, drinking fizzy drinks may help to alleviate urges to misuse alcohol.

Cognitive interventions should be introduced, as appropriate, to meet the developmental needs of the individual. One such program is the manualized R&R2ADHD program, which is suitable for young people and adults. It covers topics of relevance to both ADHD and SU/SUD, including the development of prosocial competence skills, cognitive and executive functioning skills, critical reasoning, consequential thinking, emotional control, negotiation and assertiveness skills, and social problem-solving skills[61,121-123].

Relapse and prevention: Miller and Rollnick[112] state that individuals with SU/SUD are likely to oscillate between the stages of change several times before abstinence is achieved. Relapse is common for those without ADHD, and those with comorbid ADHD may be at an increased risk[124]. This understanding needs to be built into the expectations of treatment for both the service, individual and family/carers to avoid a sense of disappointment and failure. Services can help prepare individuals for relapse incidents by helping them to develop an action plan. This should include a list of warning signs and triggers for relapses and setbacks, and strategies that they have found helpful over the course of treatment which they can use to help prevent relapse. It is advisable that individuals make a note of these strategies as they progress through treatment. Acknowledging the likelihood of relapse, the plan should include compassionate messages designed to reassure and help motivate the person to get back on track, such as "I am human, we all make mistakes, I can move forward". Contact information for personal and professional networks to access support should also be included in the plan. This may include family, friends, local support groups, nominated mentors and/or 'buddies', occupational health services and confidential services. Information contained in the plan should be in the person's handwriting using their own words as this will help them to 'own' the plan. Individuals with concurrent ADHD and SU/SUD may require 'booster' sessions after treatment has concluded[124].

Identification, assessment and treatment of ADHD in adults presenting in SU/SUD community and inpatient services

Identification: Those working in SUD services should be vigilant to ADHD as a possible comorbid diagnosis, given the high prevalence of adult ADHD among those with SUD. The inherent challenges of accurately assessing ADHD in SUD services was highlighted in group discussions. A major problem is the overlap of ADHD symptoms with intoxication and withdrawal states (*e.g.*, agitation, restlessness, impulsive behaviour, concentration difficulties) and common outcomes between the two conditions (*e.g.*, job loss, poor school performance). These factors often result in ADHD being overlooked with symptoms and impairments in functioning erroneously attributed to SU[125]. High rates of comorbidity with other conditions (*e.g.*, anxiety, depression, bipolar disorder, personality disorders and autism) may further complicate diagnosis (see Table 5). Practitioners need to be aware that identification is further complicated by individuals with ADHD developing compensatory strategies that mask symptoms and/or that limit the (negative) impact on their functioning[126].

Assessment: The consensus group recommended screening for ADHD in adults with SUD. Research suggests that the Adult ADHD Self-Report Scale (ASRS)[127] could be a viable option for screening ADHD in those with SUD in terms of its sensitivity[110]. However, research indicates a lower specificity when compared to general population data[128], resulting in higher probability of false positives. This is likely to be explained by higher prevalence of comorbid psychiatric conditions as well as deficits associated with SUD[129]. Thus, the ASRS may serve as a guide to identify individuals with SUD at high risk for ADHD diagnosis, but this should be interpreted with caution and always followed up with a comprehensive clinical evaluation to differentiate findings from associated psychopathology.

Whilst screening is recommended for everyone accessing SUD services, the consensus group noted that this is not current practice. Observable markers were considered that may trigger screening, noting that some individuals appear to function better than others under SU. In particular, some substances may have a paradoxical effect for those with ADHD (*e.g.*, illicit stimulant use has shown improvement in attentional capacity and lower psychomotor activity rather than an elating effect[130]). Discussing the reasons for use (*e.g.*, to calm, dampen hyperactivity, intrusive thoughts, sleep) may be helpful, although this may be a factor associated with several psychiatric conditions and not solely ADHD. Other markers include presenting behaviors that appear beyond SU (*e.g.*, impulsivity; evidence of chaotic SU; frequent contact with the CJS and/or from an early age; gambling and other addictions, including caffeine; rapid relapse after de-toxification, transition from in-patient or other structured environments and difficulties in engaging with services and/or maintaining treatment). Importantly, for those in the care of institutional settings, their current presentation may be misleading due to high levels of structure and routine that are typical of these environments.

Table 5 Overlapping symptoms between attention-deficit/hyperactivity disorder, substance use/substance use disorder and other psychiatric disorders

Symptom	ADHD	SU/SUD	Other psychiatric comorbidity[1]
Agitation	√	√	√
Anxiety	√	√	√
Hyperactivity	√		√
Impulsivity	√	√	√
Inattention	√	√	√
Intolerance to frustrations	√	√	√
Mood instability	√	√	√
Poor concentration	√	√	√
Poor memory	√	√	√
Restlessness	√	√	√
Risk-taking behavior	√	√	√
Sleep difficulties	√		√

[1]Anxiety, depression, bipolar disorder, personality disorders.
ADHD: Attention-deficit/hyperactivity disorder; SU: Substance use; SUD: Substance use disorder.

When assessing suspected ADHD in individuals with SUD, it important to bear in mind that substances can mimic the symptoms of ADHD (negatively affecting concentration, organization, and impulsivity)[131]. Huntley and colleagues[24] found a clinically significant reduction in self-rated ADHD symptoms when comparing evaluations a few days after admission to a detoxification unit with evaluations one week later, when individuals had been detoxified or stabilized on long-term medication. This resulted in 40% of participants no longer meeting screening criteria for ADHD. Thus, in settings that prioritize rapid detoxification and discharge, screening may not provide meaningful results. Screening in addiction services should not occur at reception/upon admission but a few weeks later as it is important to obtain a stable baseline for functioning. Should screening at reception/upon admission be service policy, it is recommended that this be followed up with a second screen. Aside from factors associated with SU or its withdrawal hampering assessment, individuals may be reluctant to divulge information and reveal vulnerabilities. They may not trust how information will be used [132].

Ideally, clinical evaluations for ADHD are best conducted during a period of sustained abstinence, or once detoxification or stabilization for substance dependency has been completed. Some authors recommend at least one month of abstinence in order to assess for ADHD symptoms reliably and accurately[133]. The group however acknowledged that this recommendation may be difficult to implement in community contexts, particularly where ADHD symptoms and associated impairments in functioning may be hindering individuals from effectively engaging with SUD services. The consensus group highlighted potential risks associated with detoxification if ADHD remains untreated, including chaotic relapses. In these cases, it is important to guard against diagnosing ADHD-like symptoms that arise because of SU in the absence of underlying ADHD.

Consensus group members noted that for both inpatient and community settings, the assessment content will be the same, although the process is likely to differ, with potentially a slower paced assessment within community settings, accounting for environmental context and time to build relationships in the community.

As discussed previously, assessment must rely on a detailed developmental history for differential diagnosis. This should include a focus on drug and alcohol-free periods of the individual's life (*e.g.*, checking whether ADHD symptoms are present during periods of abstinence and/or at time prior to onset of SU) to establish if these symptoms are primary or drug induced. It is common for adults with ADHD to have other concurrent conditions including depression, anxiety, antisocial personality disorder, emotionally unstable personality disorder, and bipolar disorder. These conditions are also highly prevalent among adults with SUD. They also share many common symptoms with ADHD. For example, emotionally unstable personality disorder and ADHD share impulsivity characteristics. It is therefore imperative that as part of a comprehensive differential diagnosis assessment, the process also looks to exclude other conditions that could better explain presenting ADHD-like symptoms. Assessing individuals with SUD for ADHD requires specific expertise in psychiatric evaluation to enable differentiation between ADHD and other psychiatric disorders. Group members highlighted the risk of

diagnostic overshadowing especially with personality disorder, when practitioners are not well-versed in neurodevelopmental disorders, indicating a need for improved training in psychiatric services.

There may be a small number of individuals with SUD who present for ADHD assessment to access prescribed stimulant medication. As highlighted in the earlier section discussing the pharmacokinetics of stimulant medication for ADHD, long-acting preparations have low abuse liability. Should individuals be seeking stimulant medication for misuse purposes, it is likely that they will be dissatisfied with the effect, as they will not obtain the 'high' that they anticipate. Practitioners should ascertain the individual's expectations of diagnosis and treatment and be mindful that for a small number of individuals, symptoms may be exaggerated and/or feigned for perceived external gain[48].

Where possible, obtaining collateral information from other sources will help to reduce the risk of misdiagnosis. Obtaining informant data on ADHD symptoms for this population however can prove difficult due to the strained interpersonal relationships that many individuals with SUD have with family and friends[24]. The person may also be reluctant to share contact information. In clinical practice, the diagnostic assessment of ADHD for persons with SU/SUD may primarily rely on self-report, despite the fact that cognitive impairments associated with SUD can compromise the reliability of retrospective recall[129]. Nonetheless, where only self-report is available, research indicates that for most cases this may be sufficient, with moderately high correlations identified between informant and self-report ratings[24]. This is increased for individuals with good insight into the condition[134]. The absence of collateral information should not delay or prevent assessment.

SUD may exacerbate ADHD symptoms by as much as 30%[90] and this may alleviate with successful SUD treatment. To prevent misdiagnosis, it is important to follow-up and continue to monitor symptoms. Within adult inpatient contexts and custodial environments, it is possible to observe individuals over a prolonged period (24/7) and record degree of restlessness, inattentiveness, impulsiveness, poor emotional regulation, and problems with self-organization. Within community settings it is similarly important to be aware of behavioral observations during appointments, although quality of information may be comparatively limited due to the environmental constraints.

Pharmacological treatment: NICE guidelines suggest that appropriately qualified healthcare professionals can, with adequate training, acquire the necessary knowledge of ADHD to support assessment and/or treatment[135]. However, the experiences of the consensus group were that in the United Kingdom some healthcare practitioners with the appropriate skills to prescribe are prevented from doing so by local commissioning arrangements and guidelines[97]. Constraining prescribing to scarce and over-stretched specialist services is unnecessarily limiting and does not reflect the range of services involved in the care of individuals with concurrent ADHD and SUD. In accordance with NICE guidelines, the consensus group agreed that expanding local commissioning parameters to allow prescribing more widely would streamline care. In turn this would help individuals to access the support they need and reduce clinical burden on specialist services, allowing them to manage more complex cases.

Some practitioners outside ADHD specialist services may be concerned about assuming responsibility for prescribing ADHD medication. For example, primary care practitioners have voiced concerns about stimulants being 'controlled drugs' and the risk of potential misuse and diversion[136] (see previous section on pharmacological treatment in the community and Figure 2 which discusses the pharmacokinetics of stimulant medication that refute this perspective). Facilitating confidence in prescribing was considered crucial with specialist SUD services deemed to have a role in providing readily available specialist advice and guidance *via* remote clinics (telephone or online). This was considered particularly important for this population where complexity issues with poly-pharmacy are likely to be encountered. Research suggests that clear protocols and clearer advice from specialist services may help to change some hesitant practitioners' views on prescribing[137]. The effectiveness of integrated care between primary care and specialist services has been demonstrated in other conditions (*e.g.* heart failure). This has shown to be associated with improved coordination between services, General practitioners (GPs) feel more confident in supporting patients, specialist services receiving more detailed feedback from primary care, and patients receiving more streamlined and holistic care[138].

When considering prescribing pharmacological treatments for this population, discussions centered on risk assessment regarding compliance and safety. In clinical practice this must be considered on an individual case by case basis (rather than categorically), and a decision made following an individual risk-benefit analysis which should be documented. Consensus group members agreed that active users of substances should still be offered pharmacological treatment if shown to be motivated to change and engaged, subject to appropriate risk assessments. Contraindications to stimulant pharmacotherapy may include current abuse of prescription stimulants or a clear indication that the medication would be sold or diverted. In addition there may be concerns regarding cardiovascular safety. Factors such as prior history of misusing stimulant medication and overall clinical stability should be considered. Practitioners should give appropriate weight to the efficacy of stimulant medication when balancing concerns regarding risk of misuse or diversion.

When considering concerns regarding misuse or diversion, the overarching opinion was that long-acting forms of stimulant medication should be prescribed. Despite lowered risk, it nevertheless remains important to be vigilant of any signs of misuse or diversion. Signs which may indicate possible

misuse or diversion include: a repeated pattern of requests to replace alleged missing or lost prescriptions; requests for dose increases (not clinically indicated); early re-ordering of prescriptions; demands for immediate release preparations or claims that long-acting prescriptions are not effective; and symptoms associated with heavier use or intoxication[89]. Individualized risk assessment should incorporate clinical management; careful monitoring is likely to detect non-therapeutic use of stimulant medication, enabling treatment plans to be modified appropriately.

Supervised consumption and interval dispensing was recommended in inpatient and custodial settings as options available to minimize risk. These should correspond with dispensing arrangements for prescribed methadone (commonly at weekly or six times per week dispensing frequencies). Consensus group members also noted that in environments which enable supervised consumption, lisdexamfetamine (a long-acting prodrug formulation) may be preferred as it can be dissolved in a drink, limiting potential for misuse or diversion. Furthermore, lisdexamfetamine has to be hydrolyzed by red blood cells to work. This means that when ingested by other routes (*e.g.*, intravenously or intranasally), the abuse potential is significantly limited. Oral and intravenous studies have shown no differences in subjective effects, likeability or blood pressure[53].

It was agreed that emphasis should be placed on adherence to the prescribed medication regimen which will facilitate optimal response. Individuals should be discouraged from binge using substances due to increased toxicity.

The consensus group highlighted the importance of ensuring that the person is part of the treatment planning process. They should feel that treatment is their choice rather than feeling it has been imposed. Educating individuals about the available treatment options including benefits and risks was considered important in helping them to develop a stake in the treatment.

Psychological interventions: Psychological treatment should address the specific difficulties experienced by adults with comorbid ADHD and SUD[139]. This involves using the same interventions discussed previously, including MI, formulation, psychoeducation, CBT, and relapse prevention approaches. The focus of treatment should include emotional liability/dysregulation, education and employment problems, interpersonal difficulties and development of prosocial competence, self-harm, dysfunctional coping strategies, and comorbid conditions such as anxiety and depression.

Psychological interventions are likely only to be effective following detoxification (*i.e.*, the individual no longer needs pharmacological treatment for withdrawal symptoms) and once the individual is stabilized[59,110]. Longer psychological support and treatment may be required for those who use opiates. It was noted that it is not uncommon for service-users to lack support of family members and/or friends due to strained relationships; these individuals may require enhanced supportive scaffolding from healthcare and service-user services.

Multi-agency interventions

Individuals with both ADHD and SUD present with complex problems and often inter-agency working is needed for the successful provision of care.

Multi-agency interventions for young people: Young people and adults with concurrent ADHD and SU/SUD may require access to coordinated ongoing support from a wide variety of agencies. Yet in the United Kingdom, there are local and regional idiosyncrasies in referral and treatment pathways for young people with ADHD that can make it difficult to access care. Some GPs are unable to refer young people suspected of having ADHD directly for an ADHD assessment. For individuals with coexisting SU/SUD (who may be or who say they are self-medicating) the problem may be exacerbated. Referrals may be managed through schools but in some cases before this can take place, parents/caregivers must complete a parenting program. If then deemed appropriate by the school, a referral for an ADHD assessment can be made. Consensus group members acknowledged that some parents who themselves have ADHD, possibly undiagnosed, (heritability of ADHD is reported to range between 70-80%[108]) may have difficulties completing a parenting program. There are potential issues with schools being gatekeepers, particularly for those with ADHD and SU, as the focus may be on the SU. As a result of this, vulnerable young people do not receive the support and/or reasonable adjustments they need (and are entitled to) in order to optimize learning and development in educational settings. This may be further complicated by the mediating role of conduct disorder[64] with young people drifting into an antisocial peer group where substance misuse is common.

Young people with ADHD are at increased risk of being suspended or expelled and dropping out of school[140]. This may be exacerbated for those with SU. If ADHD is unrecognized and undiagnosed, the possibility that these individuals may be attempting to self-medicate (deliberately or unwittingly) may not be considered. All schools should have a drugs policy establishing the ways the school will deal with drugs on school property. This needs to balance the needs of the pupils with the wider school community. In some schools this involves the establishment of a drugs contract which aims to act as a deterrent and incentive to healthy habits and decision-making. The contract is signed by the pupil and their parents or carers on a voluntary basis. Typically, the contract includes a random drug testing regime and sets prescribed sanctions for default from the contract. However, this may present a dilemma for the pupil and parents/carers regarding consent and/or ambivalence over their level of

support and co-operation with its implementation.

Community social interventions (*e.g.* such as Premier League Kicks[141] and Oasis Charitable Trust [142]) have an important role in supporting vulnerable individuals, including those with SU problems. Individuals should be signposted to services which can provide routes into education, training, employment, and steer young people away from a harmful trajectory.

Multi-agency interventions for adults: ADHD in adulthood is associated with work-related problems including impaired work performance and difficulties gaining and maintaining jobs[104]. The impairments associated with ADHD indicate that it should be regarded as a disability under the United Kingdom Equality Act 2010[143], affording individuals with certain rights and access to services. Individuals with ADHD may be entitled to reasonable adjustments in the workplace. Reasonable adjustments are assessed and provided on an individual basis. Some examples of reasonable adjustments include alterations to the workspace to reduce distractions in the environment, work schedule changes, frequent breaks, and use of technology assistance. Individuals may benefit from support in disclosing their ADHD diagnosis, particularly when they experience fear regarding occupational stigma.

However, commencing and sustaining new patterns of behaviour in an occupational setting can be difficult. From the experience of the consensus group, work-related problems may result in individuals using substances as a coping strategy which can further compound workplace difficulties. This is particularly relevant for people with ADHD who have executive functioning difficulties in planning, organizing, initiating, and completing tasks[107].

Relationships can be a useful 'vehicle for change' to help with this challenge; for example, a mentor or 'buddy' in the workplace can make it easier to facilitate completion of tasks. This principle is in Alcoholics and Narcotics Anonymous programs, where individuals are partnered with a sponsor who can offer help and guidance and provide accountability. Individuals should be sign-posted to formal groups of this nature for support with their treatment goals. In the United Kingdom, individuals may also benefit from a referral to social prescribing services. Social prescribing link workers adopt a holistic approach to wellbeing and can connect individuals to community groups and statutory services for both practical and emotional support.

The consensus group discussed anecdotal accounts of clinicians being asked to attend 'team around the family' meetings. This arises when concerns have been raised by other key professionals involved in the care of the family, resulting in clinicians being asked to complete parenting assessments. The consensus group experience was that these requests relate to a lack of awareness and stigma associated with ADHD, and this is further compounded when SU/SUD is present. This led to discussions where it was agreed that ADHD should not be considered a diagnosis that debars individuals from parenting (although severe and/or chronic substance dependency might).

Criminal justice system (CJS): ADHD and comorbid SU/SUD may increase risk that people will have contact with the CJS[144]. Research suggests that ADHD is likely to adversely impact an individual's pathway through the CJS, leading to further negative sanctions[145]. The consensus group noted that this may be particularly relevant for community treatment options, such as the Community Sentence Treatment Requirement (CSTR) program (available in England). Where a CSTR service operates, it gives magistrates and judges a sentencing option, whereby a community sentence with one or a combination of three treatment requirements can be applied: drug rehabilitation requirements (DRRs), alcohol treatment requirements (ATRs), and/or mental health treatment requirements[146]. From consensus group members' clinical experiences, individuals with ADHD may find it difficult to comply with DRRs and ATRs. This may result in individuals being in breach of requirements and in some cases lead to incarceration. Non-compliance with community options may be associated with symptoms of ADHD (*e.g.*, forgetfulness), but this may be disregarded if it is perceived that ADHD symptoms and resultant impairments in functioning represent 'bad behavior' rather than unmet needs[146]. A National Neurodiversity Lead for CSTRs has been in place, increasing awareness of ADHD and other neurodevelopmental conditions, and has demonstrated examples of good practice for reasonable adjustments which would be of value more broadly across the CJS.

It is important to ensure communication between in-reach and out-reach healthcare services working across CJS services, and improvement in the flow of medical information across these services is likely to enhance safe and effective care for those with comorbid ADHD and SU/SUD.

DISCUSSION

The co-occurrence of ADHD and SU/SUD is common. The presence of both conditions exacerbates difficulties greater than that of either condition alone and is associated with reduced treatment effectiveness. The identification and assessment of ADHD and SU/SUD is complicated not only by overlapping symptoms across the two conditions but by other highly comorbid conditions. Given the high prevalence of ADHD and SU/SUD comorbidity, the consensus highlighted that those working in SUD services should be vigilant to ADHD as a possible comorbid diagnosis, and those working in

ADHD services should be vigilant to signs of SU/SUD. Where ADHD or SU/SUD is suspected, assessment should be conducted by practitioners experienced in differential diagnosis. There is a risk of diagnostic overshadowing where practitioners are not well-versed in neurodevelopmental disorders, and vice versa, SU/SUD.

The use of psychostimulant medications in the treatment of concurrent ADHD and SU/SUD is complex. There is no published evidence of abuse of sustained release preparations, but caution is advisable when prescribing immediate release stimulant preparations[88]. This is not because appropriate use can give a high, but because immediate release stimulants are more likely to be crushed to a powder and snorted or used intravenously. Early treatment of ADHD may protect against later SU/SUD and can be useful in reducing ADHD symptoms without worsening pre-existing SU/SUD. Practitioners are encouraged to pharmacologically treat both ADHD and SU/SUD simultaneously, where practicable.

A multi-modal approach combining pharmacological treatment with psychological interventions is recommended, commensurate with studies which suggest that psychological therapy may be a useful strategy to treat SU among those with ADHD. Further research in this area is needed. Psychological interventions should adopt a transdiagnostic approach, targeting difficulties common to both ADHD and SU/SUD and should be adapted to meet the biopsychosocial needs and demands of the person.

Consensus meeting discussions continually highlighted existing inter-service barriers and fragmentation of care. In the United Kingdom, recent legislation has established integrated care systems which are partnerships that bring together local health and care organizations with the aim of providing better coordinated care to meet the needs of the people who live in the area. The consensus group stressed a need for re-evaluation of commissioning arrangements and pathways for those with coexisting ADHD and SU/SUD, offering opportunities for joint working and shared care, in turn resulting in better continuity of care.

Transition planning was considered a primary focus with group members noting that, with increasing age, biopsychosocial demands tend to increase whilst support declines. There is a stark notion that individuals 'fall off a cliff' when they turn 18. An emphasis on preventing drop out from services, especially when transitioning from child to adult services, may help prevent onset and/or escalation of SU. The provision of consistent, coordinated care over this important transitional period is vital. Developmentally appropriate healthcare provides an individualized integrated care approach which is responsive to the multiple and changing impacts of health conditions upon the individual and their goals[103]. Whilst currently primarily adopted for those with long-term health conditions, it is recommended more widely, including those with concurrent ADHD and SU/SUD.

Empowering general services was deemed vital. Training is an important step to ensure adequate knowledge and competencies for services to support monitoring and continuation of treatment under shared care arrangements. Access to foundational awareness training in ADHD (that is equivalent to the current provision of autism awareness training) was recommended. Ideally, this should be delivered to healthcare professionals including those in third sector mental health services, educational professionals, employment services, CJS workers, police, housing and homeless services, social workers, youth center workers, and GPs. It was also suggested that a similar level of awareness across services may be required for SUD.

It is hoped that this consensus can be used by practitioners across a range of disciplines to support the effective identification and treatment of individuals with concurrent ADHD and SU/SUD in order to achieve optimal outcomes. The consensus recommendations for practice are summarized in Table 6.

We need early and accurate identification and treatment of SU/SUD among young people in ADHD services, and vice versa. The delivery of appropriate interventions is likely to facilitate promising rather than harmful trajectories, leading to better outcomes at both individual and community levels. In the United Kingdom, systemic changes in commissioning arrangements, service delivery, workforce education and training are necessary if we are to effectively meet the needs of this complex group.

CONCLUSION

This review of the relevant current literature, combined with the diligence of the consensus group, has identified the most salient vulnerabilities of individuals with combined ADHD and SU. Furthermore, the consensus statement provides a structure within which the pertinent vulnerabilities can be best identified, treated, and managed by clinical and multi-agency interventions. The statement provides an important readily accessible contribution to the literature for practice, research, and evaluation of treatment effectiveness for young people and adults with combined ADHD and SU/SUD.

Table 6 Overview and practice recommendations

Recommendations
Identification and assessment
Due to the level of complexity, assessments should only be conducted by qualified healthcare professionals with appropriate training and expertise in assessing dual disorders. This may require foundation training in ADHD and SUD across the two services and/or assessments being made jointly by experts in different areas
It is critical to examine the temporal course of ADHD-like symptoms and SU/SUD. A focus on drug and alcohol-free periods may help with differential diagnosis
Symptoms of ADHD and SU/SUD may be masked for many reasons including overlapping of symptoms between disorders, other comorbid conditions (*e.g.*, personality disorder, bipolar disorder, anxiety, depression), and the individual may have developed compensatory strategies
Substances may have a countereffect for individuals with ADHD. Where individuals appear to be functioning better under SU, this may indicate possible underlying ADHD
Assessors should be aware that for those in institutional settings, current presentation may be misleading due to structure and routine minimising deficits in functioning
A comprehensive assessment should include a full developmental history, mental health history and current mental state examination, medical history, educational/employment history, social history, cognitive executive functioning difficulties, family history of ADHD and SU/SUD, in addition to other psychiatric and neurological problems. Perceived sex differences in presentation should be considered which may result in missed or misdiagnosis
Rating scales are not diagnostic. If used to screen, services should not rigidly adhere to cut-offs as this is likely to lead to high proportion of false positives and negatives
Young people presenting with an initial diagnosis of ADHD should be continually monitored through development for SU/SUD, given high rates of ADHD and SU/SUD comorbidity
ADHD assessment should not be conducted when an individual is under the influence of substances at the time of the assessment and/or when in a stage of withdrawal. Ideally, ADHD clinical evaluations are best conducted during a period of sustained abstinence or following detoxification or stabilization
When conducting the assessment with young people, it is important to consider how parents/caregivers are involved commensurate with the wishes and needs of the young person
The assessment may need to address additional physical, criminogenic, and safeguarding risks associated with SU. The person should be informed of the confidentiality of information shared and circumstances in which this will be breached
There are high rates of comorbidity associated with both ADHD and SU/SUD; the assessment should look to exclude other conditions that could better explain presenting symptoms
Follow-up and continued monitoring of symptoms is advised to prevent misdiagnosis
Practitioners should be aware of the risk of diagnostic overshadowing, which may require improved training in mental health services
Whenever possible, collateral information should be obtained from independent sources. For those with SUD, this may be difficult due to poor/strained relationships; the absence of collateral information should not unduly delay or prevent assessment
Pharmacological treatment
A nihilistic attitude to pharmacological treatment is not appropriate; active users of substances should be offered ADHD medication, subject to appropriate risk assessment
Long-acting stimulant preparations are recommended as first line treatment. Generally non-stimulants should be reserved as a second line due to relative effectiveness and concerns regarding non-compliance
Short-acting stimulant preparations are advised for a very circumscribed group (*e.g.*, in contexts where there is possibility for supervised consumption)
Abstinence of substance use is not necessary for individuals to benefit from ADHD medication, though SU should ideally be reduced/stabilized before initiating ADHD medication
For those with primary alcohol use, atomoxetine may be of specific consideration in light of research indicating effectiveness in reducing alcohol cravings
Prescribing needs to consider interactions between ADHD medication and other medications for comorbid conditions, where applicable
Practitioners should be aware of personal and family history of cardiovascular conditions. Where there are concerns regarding cardiovascular risk, a cardiologist should be consulted prior to prescribing stimulant medication
Heart rate, blood pressure and weight should be measured before initiating medications and routinely monitored during treatment; titration should be slow. Include height monitoring in CYP
Individuals with SU/SUD at time of stabilization should be considered for prioritization for assessment in ADHD services
Provision of developmentally appropriate healthcare (DAH) within services may be of benefit
Commissioning arrangements should permit prescribing beyond specialist services
In spite of lowered risk of misuse or diversion with long-acting stimulant preparations, practitioners should still be vigilant of signs including pattern of losing prescriptions, early re-ordering of prescriptions, demands for immediate release preparations or claims that long-acting prescriptions are not effective, and symptoms associated with heavier use or intoxication

Supervised consumption and interval dispensing should be considered as options to minimize risk. ADHD medication dispensing arrangements should correspond with prescribed methadone, where applicable

Psychoeducation on pharmacological treatment may help to improve adherence and engagement

Psychological treatment

Where neuropsychological testing has been conducted, the strengths and weaknesses profile should be used to inform adaptations to the treatment process

Email/text reminders from service should be used to reduce likelihood of non-attendance. Sessions may require increased frequency of sessions, with greater structure, being delivered at a slower pace in shorter duration and/or including mid-session breaks, with repetition and greater use of supplementary visual material

Individuals should be provided with a notebook which serves as a record of strategies learnt. This should be completed in the person's own writing to facilitate 'ownership', responsibility, and action

Motivational interviewing (MI) is more suitable for older adolescents and adults and is particularly helpful in the initial motivational stages (precontemplation, contemplation, preparation)

Practitioners need to be aware of the individual's current motivational stage and should monitor interest to engage in treatment throughout, adapting treatment interventions as necessary

Functional behavioral analysis should be used to help identify constructive or functional alternatives to substance use

Psychoeducation should be provided as an important part of the treatment process and should be returned to at regular intervals over the course of treatment, including key points of service and/or personal transition

Psychoeducational programs should differ for children, adolescents, and adult populations in relation to changing biopsychosocial needs and demands. They should be provided to both the young person and their family. Topics should include basic information about ADHD, the purpose and benefits of medication and non-pharmacological interventions, long-term consequences of SU (including legal consequences, misconceptions around medication increasing the likelihood of addiction, how and where to access local support

Societal connotations about SU can be disparaging; parent/carer group interventions provide a supportive environment where they can share experiences (common humanity) and assuage feelings of shame

Clear and realistic goals should be collaboratively identified and monitored using the SMART framework

Individuals should be invited to use self-reinforcement techniques (which hold personal meaning) as reminders of their goals

Reward systems should be incorporated into treatment to motivate new constructive behaviour

Cognitive behavioral therapy interventions should be adapted commensurate with cognitive and emotional functioning; there may need to be more of a focus on behavioral-oriented interventions when working with young people

Young people and adults may benefit from the R&R2ADHD program which adopts a transdiagnostic approach targeting difficulties common to both ADHD and SU/SUD

Psychological treatment should include a relapse and prevention action plan, with follow-up 'booster' sessions provided, as needed

Multiagency interventions

Signposting to services which provide routes into education, training, employment, can help to steer people away from a harmful trajectory and prevent relapse

Practitioners should be aware that individuals may lack support networks due to strained interpersonal relationships, requiring enhanced supportive scaffolding from healthcare and service-user services

Schools should have a drugs policy establishing clearly how schools will deal with SU, where appropriate, this may include a drugs contract. If deemed appropriate, schools should also screen and refer young people for assessment of ADHD

Educational and employment support services should be aware of potential challenges for individuals. Reasonable adjustments to education/workplace may be required to help individuals manage demands and prevent harmful trajectories

Healthcare services to make reasonable adjustments through offering combined appointments

Individuals to be sign-posted to alcoholics/drug addicts anonymous for support with treatment goals

Referral to social prescribing services may be helpful in connecting people with community groups and statutory services for practical and emotional support

Transition planning between child and adult services should commence early and be a primary focus

Services should not work in silos. Foundational awareness training in ADHD and SU/SUD (as individual and comorbid conditions) should be provided to key professionals across health and social care, education and justice services and third sector organizations

ADHD: Attention-deficit/hyperactivity disorder; SU: Substance use; SUD: Substance use disorder.

FOOTNOTES

Author contributions: Young S was responsible for the planning and scientific input of this consensus statement; all authors attended the consensus meeting; Cocallis K completed the first draft of the manuscript; It was substantially

revised by Young S with further input from Nutt D, Mason P and Mukherjee R; The second draft was revised and circulated by Young S and Cocallis K to all authors for comment and endorsement of the consensus; Following further feedback and amendments by Young S and Cocallis K, the final draft was circulated once more; all authors have read and approved the final manuscript.

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Abstract

BACKGROUND

Sleep breathing, one of the basic human needs, is a physiological need that affects cardiac functions, body temperature, daily vitality, muscle tone, hormone secretion, blood pressure, and many more. In the international literature, studies reported that patients have had sleep problems in the hospital since the 1990s, but no measurement tool has been developed to determine the causes of hospital-acquired insomnia in individuals. These findings suggest that sleep remains in the background compared to activities such as nutrition and breathing. Although patients generally experience hospital-acquired sleep problems, there is no measurement tool to determine hospital-acquired sleep problems. These features show the originality of the research.

AIM

To develop a measurement tool to determine the sleep problems experienced by patients in the hospital.

METHODS

A personal information form, hospital-acquired insomnia scale (HAIS), and insomnia severity index (ISI) were used to collect research data. The study population consisted of patients hospitalized in the internal and surgical clinics of a research hospital in Turkey between December 2021 and March 2022. The sample consisted of 64 patients in the pilot application stage and 223 patients in the main application stage. Exploratory factor analysis and confirmatory factor analysis (CFA) analyses were performed using the SPSS 20 package program and the analysis of moment structure (AMOS) package program. Equivalent forms method used.

RESULTS

The HAIS consisted of 18 items and 5 subscales. The Cronbach alpha values of the subscales ranged between 0.672 and 0.842 and the Cronbach alpha value of the overall scale was 0.783. The scale explained 58.269% of the total variance. The items that constitute the factors were examined in terms of content integrity and named as physical environmental, psychological, safety, socioeconomic, and nutritional factors. CFA analysis of the 5-factor structure was performed in the AMOS package program. The fit indices of the obtained structure were examined. It was determined that the values obtained from the fit indices were sufficient. A significant correlation was determined between the HAIS and the ISI, which was used for the equivalent form method.

CONCLUSION

The HAIS is a valid and reliable measurement tool for determining patients' level of hospital-acquired insomnia. It is recommended to use this measurement tool to determine the insomnia problems of patients and to adapt it in other countries.

Key Words: Insomnia; Sleeplessness; Sleep disorder; Scale development; Hospital; Hospital housekeeping

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Core Tip: Sleep, which is one of the basic human needs, is a physiological need that affects heart functions, hormone secretion, mood, psychological state and many more. Although there are studies in the international literature reporting that patients have sleep problems in the hospital since the 1990s, a measurement tool has not been developed to determine the causes of hospital-acquired insomnia in individuals. Determination of hospital-acquired insomnia causes of individuals; It will provide many benefits such as increasing the quality of care, improving mood, reducing stress levels, increasing the effectiveness of treatment, and increasing psychological resilience. In this research, a measurement tool was developed to identify the causes of hospital-acquired insomnia and to identify the causes of insomnia in hospitals or inpatient health institutions by focusing on the vital sleep activity. A measurement tool consisting of 18 items and 5 factors was developed. In addition, the literature on the factors that cause hospital-acquired insomnia was reviewed and some recommendations were made.

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INTRODUCTION

Sleep breathing, one of the basic human needs, is a physiological need that affects cardiac functions, body temperature, daily vitality, muscle tone, hormone secretion, blood pressure, and many more. With these properties, sleep is the basic need for human survival[1-3]. Some conditions such as pregnancy, stress, menopause, physical diseases, and hospitalization increase the need for sleep[1,4]. Sleep plays an important role in maintaining health and recovering diseases[1,3]. Moreover, sleep is a need that people are most vulnerable to deprivation and must inevitably be replaced[2].

Insomnia can be defined as difficulty falling asleep, maintaining or ending sleep, and situations in which individuals do not feel rested or ready for the new day because they do not sleep enough or for a sufficient time[1,2]. Insomnia can occur independently or due to other problems. Temporary insomnia, which may arise from reasons such as stress, is a common problem, including in hospitals. Studies show that 33% to 69% of patients experience sleep deprivation in the hospital[5-7].

Insomnia is a common patient complaint during hospitalization[8-12]. While in the hospital, patients may experience sleep problems due to many reasons such as hospitalization, not getting used to the bed, being away from the family, a foreign environment, disease anxiety, surgical interventions, sound, light, noise, inability to meet the needs of daily living, and deterioration in body image[13,14]. In addition, it is stated that some factors such as the high number of patients in the room, room temperature, implementations made at sleep time, and the obligatory sleeping positions affect sleep patterns in the hospital[15]. It is stated that the reasons such as the stuffiness of the room, smell, reasons arising from the bedding, inconvenience of the bed and the pillow, pain, lack of information, drugs, tubes such as drains-catheters, hunger-fullness also cause sleep problems among hospitalized patients [16]. In another study, it was stated that in intensive care units, sleep is affected by factors originating from intensive care (noise, patient care, and treatment practices) and disease-related factors (pain,

anxiety, disease severity, drugs, mechanical ventilation)[17].

Individuals resort to medication since insomnia creates stress and anxiety in individuals. However, in this process, it will be a more effective method to determine the cause of insomnia, take precautions, eliminate the cause, make necessary arrangements for sleep, plan the nursing care accordingly, and use medication as a last resort[2,18,19]. The ability of a nurse to solve this problem is associated with his/her ability to evaluate sleep and the appropriateness of the measurement tools used.

According to the literature, scales such as the Epworth sleepiness scale[20], Pittsburg sleep quality index[21], DSM-5 sleep-wake disorders module[22], Richard-Campbell sleep questionnaire[23], postpartum sleep quality scale[24], sleep quality scale[25], Jenkins sleep scale[26], sleep hygiene index [27], sleep assessment scale for children with cancer[28] are used to determine sleep-related problems in our country. In addition, the form of factors affecting sleep[29] is used to evaluate sleep in terms of quantity and quality. As can be understood from the names of the scales, there is no measurement tool to measure the causes of hospital-acquired insomnia. In the international literature, studies reported that patients have had sleep problems in the hospital since the 1990s, but no measurement tool has been developed to determine the causes of hospital-acquired insomnia in individuals. These findings suggest that sleep remains in the background compared to activities such as nutrition and breathing. This research focuses on the activity of sleep, which is vital and aimed to develop a measurement tool to reveal the causes of hospital-acquired insomnia and determine the causes of insomnia in hospitals or inpatient health institutions. In addition, literature on the factors that cause hospital-acquired insomnia was reviewed and some recommendations were made. These features show the originality of the research.

MATERIALS AND METHODS

Research type

The research was designed as a methodological study.

Research place and time

The study was conducted with patients hospitalized in surgical and internal medicine clinics in a research hospital in Turkey between December 2021 and March 2022.

Research population and sample

The population of the study consisted of patients hospitalized in Turkey. During the pilot application of the study, 64 patients were reached. It is stated that the sample size should be at least 5 times the number of scale items (10 times if possible) in scale adaptation studies[30]. The main application stage started with 42 items. For this reason, it was predicted that the sample size should have been at least 210 or 420. Therefore, 223 patients were reached during the main application stage. The data were filled in using the face-to-face interview method. It took 20-30 min to fill in the data of each patient. The study was completed with a total of 287 patients.

Inclusion criteria of research

(1) Not having any sleep problems before hospitalization; and (2) Being hospitalized for at least three days.

Data collection tools

The data were collected using a personal information form and the hospital-acquired insomnia scale (HAIS)-draft form.

Personal information form: This form consists of questions about gender, age, education level, social security, and previous hospitalization of the participants.

Insomnia severity index: The index was developed by Bastien *et al*[31] in 2001 and was validated in Turkish by Boysan *et al*[32] in 2010. The 7-item index was developed in a 5-point Likert type in order to measure the degree of insomnia of individuals. Items are scored between 0-4; the lowest score obtainable from the scale is 0 and the highest score is 28. In scoring, a score of 0-7 indicates clinically insignificant insomnia; 8-14 indicates insomnia lower threshold; 15-21 indicates clinical insomnia (moderately severe); 22-28 indicates clinical insomnia (insomnia) (severe). Insomnia severity index (ISI) was used to determine the concurrent validity of the scale. Concurrent validity is the comparison of the findings obtained from a measurement tool that is desired to be developed with a scale, whose validity and reliability has been proven, on a similar subject. A correlation is expected between the data obtained from both measurement tools[33].

HAIS: First stage: The relevant literature was examined in depth. Interviews were held with 2 patients, 2 patient relatives, and 4 nurses about the causes of hospital-acquired insomnia. After the literature

review and interviews, a conceptual infrastructure on the subject was created. An item pool of 150 items considered suitable for the scale was prepared. The item pool was reviewed 4 times and some items were eliminated. The item pool was finalized with 66 items for expert opinion.

Second stage: The item pool consisting of 66 items was presented to 11 experts (2 Turkish language experts, 9 field experts) and the content validity was evaluated. The items in the scale were revised in line with expert opinions. Then, the suitability of the scale items was evaluated, the Turkish language validity was established, and the revisions were completed. 10 items were removed from the scale. The scale was finalized for the pilot application with 56 items. The Cronbach alpha value of the data of 56 items was determined as 0.882. In the pilot application stage, 14 items (i4, i6, i9, i12, i14, i19, i22, i26, i29, i30, i32, i35, i36, i43) with an item correlation value of less than 0.20 were removed from the item pool. The Cronbach alpha value was determined to be 0.913 with 42 items. Main application stage started with 42 items.

Third stage: Validity and reliability analysis of the HAIS was performed. The sample of the study consisted of 223 patients. In the analyses, it was determined that the scale is a valid and reliable measurement tool consisting of 18 items and 5 subscales. The scale was developed as a 5-point Likert scale (1: Strongly disagree - 5: Strongly agree). Scoring for the subscales and the overall scale was based on the item score average. The lowest score obtainable from the scale and its subscales is 1 and the highest score is 5. There is no reverse item on the scale. As the scale score increases, hospital-acquired insomnia increases. There is no cut-off point in the scale. The Cronbach alpha value for the overall scale was determined to be 0.783.

Pilot application

In scale adaptation studies, it is necessary to reach a sample size of more than 50; the internal consistency of the scale should be 0.70 and above; it should be checked whether the item-total correlation value is below 0.30[34]. In this study, the pilot application was carried out with 64 patients. In the pilot application stage, 14 items with an item correlation value below 0.20 were removed from the item pool. The Cronbach alpha value was determined to be 0.913 with 42 items and the main application stage was initiated.

Main application

The patients were visited in their rooms and their informed consent was obtained. After their consent was taken, the data of the study were collected by the face-to-face method. The scale items were asked to the patients one by one by the researcher (BÇ) and their answers were marked. At this stage, the HAIS and the ISI, which is thought to be a parallel form, were used. In the main application, 223 patients were reached. At this stage, validity and reliability analyses, two criteria that a scale should have, were performed[35].

Statistical analysis

SPSS 20 package program and analysis of moment structure (AMOS) 20 package program" were used for data analysis. Frequency and percentage were used to indicate the sociodemographic characteristics of the patients. Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were used to ensure scale validity. In the EFA, item score averages and standard deviations, Kaiser-Meyer-Olkin (KMO), Bartlett's test of sphericity, item-total correlation value was used. Scree plots chart and eigenvalue were used to determine the factor structures of the scale[34,36,37].

KMO and Bartlett's sphericity tests were performed to check the suitability of the sample size and the suitability of the data set for analysis. The fact that the KMO test was greater than 0.60 and the *P* value of the Barlett's sphericity test was significant showed the adequacy of the sample and the suitability of the data set[34,38,39].

EFA was performed to ensure construct validity. During the EFA, there should be no overlapping items. In addition, the item eigenvalue of the scale items should be at least 1 and the item load should be at least 0.30[34,40]. Varimax rotation, which is a vertical rotation method preferred in scale development studies, was used to ensure construct validity[34,36]. The presence of multicollinearity problem was tested with linear regression [variance inflation factors (VIF) < 10, C-index (CI) < 30, tolerance > 10][38]. If an item has a loading value of more than 0.32 in more than one dimension and the difference between factor loadings in these dimensions is less than 0.10, these items were accepted as overlapping items[34].

In CFA, fit indices and path diagram were used. The Cronbach alpha value of the items, factors and total scale was used to determine the reliability level of the scale. In addition, split half analysis was performed. Retest method was used to determine the invariance of the scale against time. The following criteria were taken as basis: a minimum KMO value of 0.60, a Bartlett's test of sphericity *P* value being significant, an eigenvalue of at least 1, a Cronbach alpha value of at least 0.7 for factors and the scale, a split half Cronbach alpha value of at least 0.7. The values suggested by Bae *et al*[41], Woo *et al*[42] were taken into account in the fit indices [χ^2/SD value, goodness of fit index (GFI), adjusted GFI, comparative fit index, root mean square error of approximation, standardized root mean square residual fit indices] [41,42].

In the analyzes related to reliability, a Cronbach alpha value of 0.70 and above was taken as the basis [43-45].

Ethical aspects and permissions

Ethics committee approval dated 16.08.2021 and numbered 20028 was obtained from the Muş Alparslan University Scientific Research and Publication Ethics Committee. Institutional permission was obtained from Atatürk University Research Hospital in order to carry out the study. Patients were informed about the purpose and method of the study and that the research was based on volunteerism in detail. Consent was taken from the patients participating in the study. The individuals participating in the research were informed that their data would not be shared.

RESULTS

Of the patients, 52% were famale; 47.1% were aged between 51-70; 49% were primary school graduates; 69.5% had social security; 30.9% had a history of 1-2 wk-hospitalization; the sleep quality of 31.8% was between 7 and 8 (Table 1).

Validity findings

EFA: Reliability analysis was performed to determine whether the items had appropriate values. Therefore, 11 items were removed before starting the EFA. EFA was performed to ensure construct validity. In order to determine the items to be included in the scale, it was taken into account that there was no overlapping item, the item eigenvalue was 1, and the item load value was at least 0.30. The Cronbach alpha value of the remaining 31 items was determined to be 0.783. The analysis was continued with 31 items. Varimax axis rotation, a vertical rotation method preferred in scale development studies, was used in order to ensure construct validity.

Before performing exploratory and CFA for the scale, KMO and Bartlett's sphericity tests were performed to check the suitability of the sample size and the suitability of the data set for analysis. In addition, the anti-image test, which is one of the sampling criteria, was applied. The KMO value was determined as 0.663. Bartlett's sphericity test was found to be significant (χ^2 = 3019.015; P = 0.001) (Table 2). As a result of the anti-image test, it was determined that there was no value below 0.50. These results showed that the sample size and data set were suitable for analysis.

Items i4, i5, i6, i13, i18, i19, i20, i23, i24, i28, i30, i39, and i40 were excluded from the scale since they were overlapping items. In the EFA performed with 18 items, it was determined that the KMO value was 0.741 and that Bartlett's sphericity test was significant (χ^2 = 1704.892, P = 0.001). The anti-image test was examined and it was found that there was no value below 0.50. These findings showed that the data were suitable for factor analysis. As a result of the Varimax analysis, it was determined that the scale items were gathered under 5 factors. The scree plot also confirmed that the scale has a 5-factor structure. In light of this information, CFA was performed with 5 factors and 18 items (Figure 1).

When the analysis results were examined, it was found that factor 1 consists of 5 items, i22, i26, i29, i31, i32, and explained 22.345% of the total variance. This factor was named physical environmental factors.

Factor 2 consists of 4 items, i7, i14, i15, i16, and explained 18% of the total variance. This factor was named psychological factors.

Factor 3 consists of 3 items, i41, i42, i43, and explained 11.016% of the total variance. This factor was named safety factor.

Factor 4 consists of 3 items, i10, i11, i12, and explained 8.580% of the total variance. This factor was named socioeconomic factors.

Factor 5 consists of 3 items, i1, i2, i3, and explained 5.788% of the total variance. This factor was named nutritional factors.

When the 18-item scale was analyzed as a whole, it was determined that it has a 5-factor structure and that the common factor loads of 18 items varied between 0.407 and 0.886. It was determined that 5 factors explained 66.25% of the total variance. These values showed that the scale is sufficient to explain the hospital-acquired insomnia problems of patients (Table 3).

CFA: The structure obtained from EFA was tested with CFA. In line with the modification recommendations made with CFA, it was deemed appropriate to make modifications between items i10-i12 and i22-i29. After modification, improvements were observed in the χ^2 value. Information on the fit indices obtained as a result of CFA is given in the table. Fit values were evaluated considering the reference values stated. (Table 4) The items were considered important for the factors in which they were included. The path diagram was examined and it was determined that the obtained values were appropriate in terms of the item-factor agreement (Figure 2).

Reliability findings

Internal consistency (Cronbach alpha) coefficients: The Cronbach alpha coefficient was calculated to

Table 1 Distribution of patients by sociodemographic characteristics (*n* = 221)

Characteristics	Variables	*n*	%
Sex	Famale	116	52
	Male	107	48
Age	18-30	16	7.2
	31-50	50	22.4
	51-70	105	47.1
	71 and above	52	23.3
Educational status	Illiterate	45	20.2
	Primary school	110	49.3
	Middle school	20	9
	High school and above	48	21.5
Social security	Yes	155	69.5
	No	68	30.5
Hospitalization	No	44	19.7
	Less than 1 wk	57	25.6
	1-2 wk	69	30.9
	2-3 wk	23	10.3
	1 mo and more	15	13.4
Sleep quality with 1 lowest 10 highest	1-2	21	9.4
	3-4	38	17.1
	5-6	49	22
	7-8	71	31.8
	9-10	44	19.8

Table 2 Cronbach's alpha, Kaiser-Meyer-Olkin values and Bartlett's test results for data sets

Tests		Test results
Kaiser-Meyer-Olkin sampling adequacy		0.663
Bartlett's test of sphericity	χ^2	3019.015
	Standard error	465
	P value	0.001

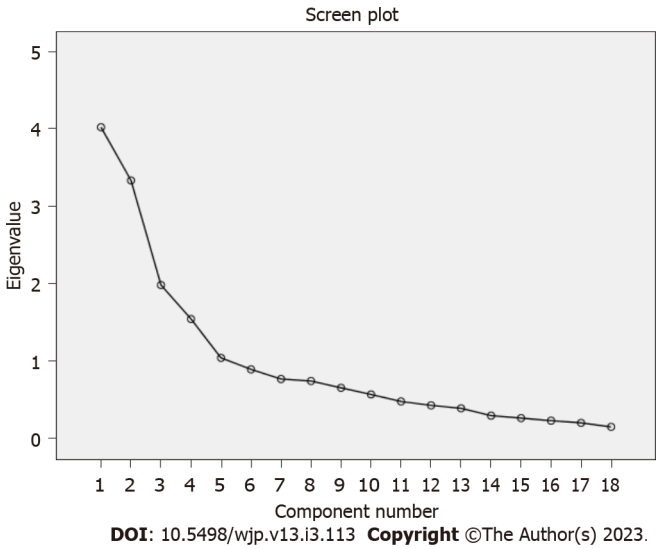
determine the reliability analysis of the 18 items of the finalized scale. The Cronbach alpha values were 0.672 for the nutritional factors subscale including items i1, i2, and i3; 0.677 for the socioeconomic factors including items i10, i11, i12; 0.804 for the psychological factors subscale including items i7, i14, i15, and i16; 0.842 for the physical environmental factors subscale including items i22, i26, i29, i31, i32; 0.786 for the safety factors subscale including i41, i42, and i43. The Cronbach alpha value for the overall scale was 0.783. These values show that the scale is reliable.

Split half confidence coefficient: As a result of the split half reliability analyses of the 18-item final version of the scale, it can be said that the Spearman-Brown correlation value (r = 0.670) and the Guttman split half coefficient value (r = 0.60) of the scale have sufficient values and that the Cronbach alpha reliability coefficients for the split halves are sufficient. The split half reliability coefficients are given in the table (Table 5). The results of the split half reliability analyses showed that the scale is reliable (Table 5).

The item score means were determined to be 1.06 ± 032 for F1, 1.57 ± 0.90 for F2, 1.12 ± 0.46 for F3, 1.41 ± 0.77 for F4, and 1.08 ± 0.27 for F5. The item score mean of HAIS was 1.25 ± 0.35. The mean total ISI score was determined to be 10.35 ± 7.76 (Table 6).

Table 3 Hospital-acquired insomnia scale exploratory factor analysis results

	Common load value	Faktors				
		1	2	3	4	5
i31	0.781	0.869				
i26	0.758	0.865				
i32	0.713	0.843				
i22	0.567	0.733				
i29	0.554	0.729				
i16	0.781		0.855			
i15	0.727		0.815			
i14	0.662		0.666	0.339		
i7	0.485		0.647			
i41	0.886			0.924		
i42	0.758			0.835		
i43	0.572			0.696		
i11	0.704				0.783	
i12	0.552				0.705	
i10	0.666		0.392		0.680	
i3	0.747					0.855
i2	0.604					0.774
i1	0.407					0.631
Eigenvalue (total = 11.925)		4.022	3.334	1.983	1.544	1.042
%Total explained variance = 66.250%		22.345	18.521	11.016	8.580	5.788



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Figure 1 Scree plot factor structure.

It was determined that there was a positive and significant correlation between the mean ISI score and the mean scores on F2, F3, F4, and HAIS. A statistically significant correlation was found between HAIS and F1, F2, F3, F4, and F5. These findings show that the scale is an adequate tool to measure the hospital-acquired insomnia levels of patients (Table 7).

Table 4 Confirmatory factor analysis goodness of fit indices and normal values

Index	Normal value	Acceptable value	Measurement	Result
χ^2/P Value	> 0.05	-	0.001	Perfect fit
χ^2/SD (CMIN/DF)	< 2	< 5	1.874	Perfect fit
GFI	> 0.95	> 0.90	0.900	Acceptable fit
AGFI	> 0.95	> 0.85	0.861	Acceptable fit
CFI	>0.95	> 0.90	0.933	Acceptable fit
RMSEA	< 0.05	< 0.08	0.0.070	Acceptable fit
RMR	< 0.05	< 0.08	0.039	Perfect fit
SRMR	< 0.05	< 0.08	0.0600	Acceptable fit
NFI	> 0.95	> 0.80	0.869	Acceptable fit
TLI	0.95 < TLI < 1	0.90 < TLI < 0.94	0.917	Acceptable fit
IFI	> 0.90	-	0.934	Perfect fit
PGFI	> 0.89	> 0.50	0.648	Acceptable fit
PNFI	> 0.89	> 0.50	0.699	Acceptable fit

CMIN/DF: Chi-square fit statistic/degree of freedom; GFI: Goodness of fit index; AGFI: Adjusted goodness of fit index; CFI: Comparative fit index; RMSEA: Root mean square error of approximation; RMR: Root mean square residual; SRMR: Standardized root mean square residual; NFI: Normed fit index; TLI: Tucker–Lewis index; IFI: Incremental fit index; PGFI: Parsimony goodness of fit index; PNFI: Parsimony normed fixed index.

Table 5 Results of two-half confidence analysis

Two half	Cronbach alpha
Part 1	0.738
Part 2	0.606

Table 6 Mean score of the hospital-acquired insomnia scale and its sub-dimensions

	Average	SD	Min	Max
F1	1.06	0.32	1.00	5.00
F2	1.57	0.90	1.00	5.00
F3	1.12	0.46	1.00	4.00
F4	1.41	0.77	1.00	5.00
F5	1.08	0.27	1.00	3.00
Total hospital-acquired insomnia scale	1.25	0.35	1.00	3.06
Insomnia severity index	10.35	7.76	0	28

DISCUSSION

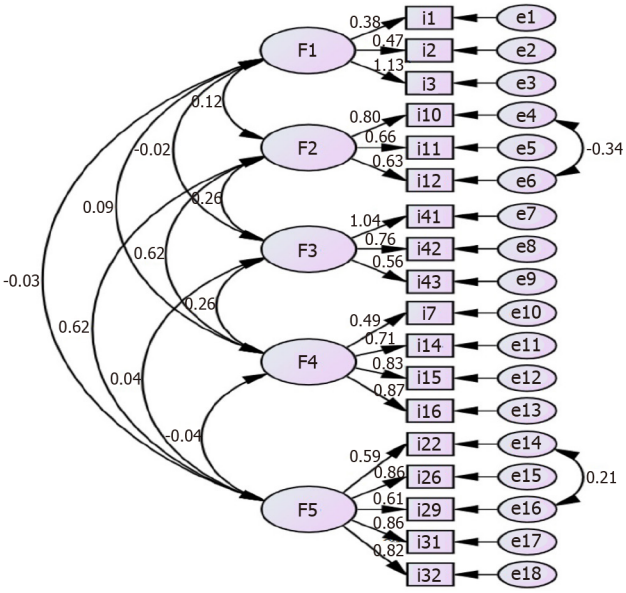
In order to create the conceptual structure of the scale and prepare the item pool, the literature was reviewed and in-depth interviews were conducted with 2 patients, 2 patient relatives, and 4 nurses. An item pool of 150 items was created. The item pool was reviewed 4 times and an item pool of 66 items was created to be presented to experts. Two Turkish language experts and 9 field experts were consulted. In line with the recommendations of 11 experts, 11 items were removed from the item pool and the pilot application started with 56 items. During the pilot application stage, 64 patients were reached. In line with the data obtained from 64 patients, 14 items were excluded since the total correlation value was low and the main application stage was initiated with 42 items.

During the main application stage, 223 individuals were reached. Reliability analyses were performed in line with the data obtained from 223 individuals and 11 items with low item correlation values were

Table 7 Relationship between the hospital-acquired insomnia scale and its sub-dimensions and the insomnia severity index

	F1	F2	F3	F4	F5	HAIS
Insomnia severity index						
r	-0.079	0.378[1]	0.226[1]	0.208[1]	-0.061	0.334[1]
P value	0.242	0.000	0.001	0.002	0.361	0.000
Total hospital-acquired insomnia scale						
r	0.303[1]	0.886[1]	0.343[1]	0.705[1]	0.281[1]	1.000
P value	0.000	0.000	0.000	0.000	0.000	-

[1]Correlation is significant at the 0.01 level (2-tailed).
HAIS: Hospital-acquired insomnia scale.



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Figure 2 Clinical application readiness scale confirmatory factor analysis diagram.

eliminated from the analysis. As a result of the EFA performed with 31 items, 13 items were excluded from the analysis one by one since they were overlapping. While each item was removed from the analysis one by one, KMO, Bartlett's sphericity test, and anti-image test were checked. The overlapping status was checked and items were removed accordingly. Bartlett's sphericity test, KMO value, and anti-image test were checked with the remaining 18 items. Bartlett's sphericity test ($P < 0.05$), KMO value (0.741), and anti-image test for 18 items were found to be suitable for analysis[33-35]. As a result of the EFA of 18 items, a 5-factor structure was created. Scree plot also showed that the structure consisted of 5 factors. The items that constitute the factors were examined in terms of content integrity and named as physical environmental, psychological, safety, socioeconomic, and nutritional factors. CFA analysis of the 5-factor structure was performed in the AMOS package program. The fit indices of the obtained structure were examined. It was determined that the values obtained from the fit indices were sufficient. These results revealed that the scale is valid and reliable.

With the keywords "sleep" and "insomnia", national and international literature was first searched on the Turkish measurement tools index and Google scholar. 20 relevant scales were reached. Eight scales were found to be regarding adult patients or associated with the hospital. The names of these scales were as follows; Pittsburgh sleep quality index[21], Epworth sleepiness scale[20], insomnia severity index[31], Richard-Campbell sleep questionnaire[23], DSM 5 sleep-wake disorders scale[22], Thought control questionnaire-insomnia revised[46], insomnia catastrophizing scale[47]. All scales were examined one by one and it was determined that there was no tool to determine hospital-acquired sleep problems. In addition, the subscales of the scales in question and the subscales of the hospital-acquired insomnia scale, which is the subject of the research, were examined and no similarity was detected. This shows the originality of the scale. It was determined that the Cronbach alpha values of the subscales ranged between 0.672 and 0.842 and the Cronbach alpha value for the overall scale was 0.783. It was

determined that the scale explained 58.269% of the total variance.

Practice implications

It is stated that patients who do not have sleep problems in their daily routine at home have problems after hospitalization, such as waking up frequently, having difficulty falling asleep, decreased sleep time, not feeling rested when they wake up, and inability to sleep. A new environment, the severity of the underlying disease, underlying psychiatric conditions, pain, room light, sharing a room with others, being away from the family, changes in sleep-wake-up times, pain, bad condition of the roommate patient, worrying about the disease, inadequate physical activity, frequent entries to the room, medications, and infections.

Hospital-acquired insomnia is usually treated symptomatically at the time of hospitalization. However, misuse or overuse of sedatives/hypnotics is thought to be associated with complications in this population of acute patients. The use of a scale to determine the causes and severity of insomnia before resorting to pharmacological methods is one of the indicators of quality nursing care. Prevention of hospital-acquired insomnia, which is evaluated with the scale, with simple and applicable nursing interventions will contribute to the prevention of unnecessary use of medications.

CONCLUSION

In conclusion, the scale consists of 18 items and 5 subscales: Physical environmental factors, psychological factors, safety factors, socioeconomic factors, and nutritional factors. The subscale of physical environmental factors consists of 5 items; psychological factors consist of 4 items; safety factors, socioeconomic factors, and nutritional factors subscales consist of 3 items. There is no reverse item on the scale. The item score average is used in the calculation of the scale score. The lowest score obtainable from the scale and 5 subscales is 1 and the highest score is 5. There is no cut-off point in the scale. As the scale score increases, the hospital-acquired insomnia level increases. The scale explains 66.250% of the total variance. In the light of this information, it can be said that the hospital-acquired insomnia scale is a valid and reliable measurement tool.

ARTICLE HIGHLIGHTS

Research background

Insomnia is a major problem for people. Many causes of insomnia have been reported. One of these reasons is hospital-acquired insomnia. Although it has been stated in many studies that patients experience hospital-acquired insomnia, it has been determined that there is no valid and reliable measurement tool that measures hospital-acquired insomnia problems of individuals.

Research motivation

Insomnia, which affects individuals physiologically, psychologically and therapeutically, is a serious problem in the hospital. Hospital-induced insomnia affects the quality of treatment and care. For this reason, healthcare professionals need a measurement tool that can measure the hospital-acquired insomnia levels of patients.

Research objectives

In this study, it was aimed to develop a valid and reliable measurement tool that can determine the hospital-acquired insomnia levels of patients.

Research methods

This research is scale development research consisting of a pilot application and a main application. First of all, an item pool was created for the scale and presented to expert opinion. After the expert opinion, the scale items were made ready for pre-application. In the preliminary application, data were obtained from 64 individuals. During the main application phase, 223 patients were reached. Exploratory factor analysis, confirmatory factor analysis and reliability analyzes were performed with the obtained data. Analyzes were performed using SPSS 20 package program and analysis of moment structure package program.

Research results

As a result of data analysis, it was determined that the scale consisted of 5 sub-dimensions and 18 items. The total Cronbach alpha value of the scale was determined to be 0.783.

Research conclusions

It was determined that the scale, which consists of 5 sub-dimensions and 18 items, is a valid and reliable measurement tool in determining the hospital-acquired insomnia levels of the patients.

Research perspectives

It is recommended to use this measurement tool to determine the insomnia problems of patients and to adapt it in other countries.

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FOOTNOTES

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CASE REPORT

Tardive sensory syndrome related to lurasidone: A case report

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Abstract

BACKGROUND

Tardive sensory syndrome (TSS) is a subtype of tardive syndrome (TS), and its etiology is still uncertain. Lurasidone is an atypical antipsychotic that has high affinity for dopamine D2- and serotonergic 5HT2A- and 5-HT7-receptors.

CASE SUMMARY

A 52-year-old woman, previously diagnosed with schizophrenia, and with no history of movement disorders and no sensory paresthesia, had taken lurasidone, initiate dose 40 mg daily then up titration to 120 mg daily, since March 2021, and developed mandibular sensory (pain) paresthesia after 3 mo of administration. After switching from lurasidone to quetiapine, she reported obvious improvement in her mandibular pain.

CONCLUSION

It is noteworthy that TSS is a rare subtype of TS, and lurasidone, an atypical antipsychotic, usually has a lower risk of causing TS. In light of the temporal relationship, it is therefore concluded that use of lurasidone might have caused TSS in this patient. We reported this rare case as a reminder that clinicians should adopt a cautious approach when prescribing atypical antipsychotics, so as to prevent TS.

Key Words: Antipsychotic; Tardive syndrome; Tardive sensory syndrome; Lurasidone; Case report

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Core Tip: Tardive sensory syndrome is a subtype of tardive syndrome (TS), and its etiology is still uncertain. Lurasidone is an atypical antipsychotic that has high affinity for dopamine D2- and serotonergic 5HT2A- and 5-HT7-receptors. We reported a 52-year-old woman with schizophrenia developed mandibular sensory (pain) paresthesia after 3 mo of administration of lurasidone. This case report reminds clinicians should adopt a cautious approach when prescribing atypical antipsychotics, so as to prevent TS.

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INTRODUCTION

Tardive syndrome (TS) is an iatrogenic condition resulting from exposure to chronic dopamine receptor blocking agents (DRBA), and is a more expansive phenomenological spectrum that encompasses tardive dyskinesia (TD), tardive dystonia, tardive akathisia, tardive sensory syndrome (TSS), tardive parkinsonism, and tardive tics[1]. TS is a distressing adverse effect of medication that might impair patients' quality of life and even increase the risk of suicide[2]. Lurasidone is an atypical antipsychotic that exerts its effects through high affinity for dopamine D2- and serotonergic 5HT2A- and 5-HT7-receptors[3]. To our knowledge, there is no report of TSS as a side effect of lurasidone in the literature. Here, we describe a patient with schizophrenia who had been treated with lurasidone for 3 mo, and later developed TSS.

CASE PRESENTATION

Chief complaints

A 52-year-old female developed mandibular sensory paresthesia and pain after 3 mo of lurasidone administration, without orofacial dyskinesia, hands tremor, limbs rigidity, bradykinesia, axial dystonia, retrocollis, torticollis, or blepharospasm.

History of present illness

A 52-year-old female had been diagnosed with schizophrenia since April 2001, and was treated with various antipsychotics, including risperidone 1 mg/d, amisulpride 200 mg/d, quetiapine 200 mg/d, ziprasidone 40 mg/d, and clozapine 125 mg/d, with a duration of a few months, respectively. The most long duration of main regimen was olanzapine 10-25 mg daily (June 2013-March 2021), which was fully effective, but was discontinued due to the adverse side effect of weight gain. Consequently, the main regimen was shifted to lurasidone, initiate dose 40 mg/d then up titration to 120 mg/d since March 2021. However, she developed mandibular sensory paresthesia and pain after 3 mo of lurasidone administration, without orofacial dyskinesia, hands tremor, limbs rigidity, bradykinesia, axial dystonia, retrocollis, torticollis, or blepharospasm.

History of past illness

A 52-year-old female with no history of medical disease, movement disorders or sensory paresthesia had been diagnosed with schizophrenia since April 2001.

Personal and family history

The patient had no developmental delay, and had elementary school education level with poor academic performance. She had introverted personality as premorbid personality and poor interpersonal relationship. She could keep her occupational function as a cleaner since young adult until now. She got married at her 20's and divorced at her 32' while she was diagnosed of schizophrenia. The patient denied psychiatric family history.

Physical examination

We also consulted a dentist to rule out oral infection or other lesions. Both the aforementioned laboratory tests and dental consultation showed negative findings. Due to the defining features, TSS was suspected[4]. Severity was evaluated on the basis of an Extrapyramidal Symptom Rating Scale (ESRS) score of 18 points[5] before we changed antipsychotics to quetiapine monotherapy.

Laboratory examinations

A series of laboratory tests including complete blood count, liver function, renal function, diabetes mellitus lipid profile, copper, ceruloplasmin, thyroid function, rheumatoid factor, antinuclear antibody, immunoglobulin (Ig)A, IgG, anti-2 glycoprotein 1Ab, anticardiolipin Ab IgG, anticardiolipin Ab IgM. Anti-ENA, a venereal disease research laboratory test, HBs antigen, hepatitis C virus antibody, cryoglobulin identification, a homocysteine test and brain computed tomography (CT), were performed to rule out a secondary organic etiology. We also consulted a dentist to rule out oral infection or other lesion. The aforementioned laboratory tests and dental consultation both showed negative findings.

Imaging examinations

The brain CT image and report are demonstrated in Figure 1. Technique of examination: Axial brain CT with 5 mm section from vertex to skull base without contrast enhancement; normal ventricular size; normal appearance of cerebral fissures, cisterns & sulci; no evidence of intracranial hemorrhage; no midline deviation; no abnormal parenchymal attenuation change; no definite bony fracture; well pneumatization of bilateral mastoid cells; unremarkable of paranasal sinus; symmetrical and smooth contours of nasopharynx; and left frontal scalp swelling. There is no evidence of intracranial hemorrhage.

FINAL DIAGNOSIS

Due to the defining features, TSS was suspected[4] (see Video).

TREATMENT

After lurasidone was switched to quetiapine 300 mg/d, the aforementioned sensory discomfort was significantly ameliorated, and remission was achieved.

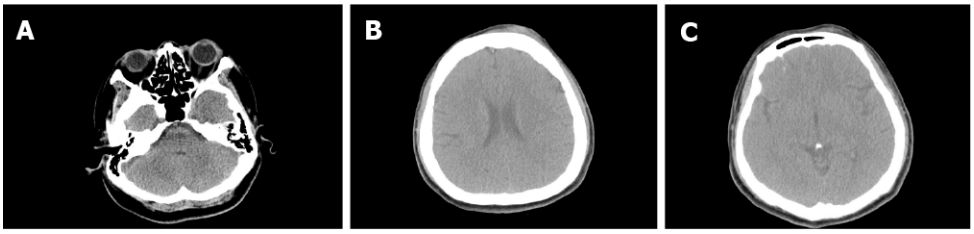
OUTCOME AND FOLLOW-UP

After 1 mo, the ESRS scores improved by 65% (from 18 to 6); at the outpatient clinic follow-up, the visual analog scale scores for pain measurement decreased to 0/10 after 6 mo in remission.

DISCUSSION

TSS, manifested with unpleasant, burning or pain sensation in the oral or genital regions, is a chronic and specific type of TS. However, the pathophysiology of TSS remains uncertain[6]. D2 hypersensitivity alone seems to be insufficient to account for TS, or TSS. One theory has been proposed to elucidate the pathophysiology of TS; some atypical agents (clozapine and quetiapine in particular) have a relatively low affinity for D2 receptors that loosely bind to postsynaptic D2 receptors in the striatum then dissociate quickly, but some DRBAs act as binding tightly and have long-lasting effects on the receptors [7], which may explain why remission of TS is achieved after cross-shifting of lurasidone to quetiapine, as in our case. Another explanation for TS is that TS is attributed to defective adaptation of 5-HT2A, vesicular monoamine transporter type 2 levels, metabotropic and N-methyl-D-aspartatic acid receptors in the striatum, that as demonstrated in effect of antipsychotic drugs on nonhuman primates[7]. In addition, both pro- and antinociceptive effects of 5-HT2A receptor activation likely appear in other studies, but converging evidence underscores that peripheral 5 HT-2A receptors have an excitatory role in acute, sub-chronic and chronic pain transmission[8,9].

That then is another reasonable explanation why the remission of TS was achieved after cross-shifting of lurasidone to quetiapine in this case. A similar explanation may have been offered in a previous report of TSS related to trazodone which is a potent serotonin 5-HT2A and 5-HT2C receptors antagonist and a weak serotonin reuptake inhibitor that results in more dopamine release[10]. An alternative hypothesis, supported by human and animal neuropathological studies, indicates that TS is a neurodegenerative disorder involved in striatal interneurons damaged by oxidative stress. This theory assumes that dopaminergic receptor blockade may lead to elevated turnover rates of dopamine and free radical produced by monoamine oxidase[6]. Eleven cases of TSS associated with antipsychotic drugs have been reported, and each case suffered from profound pain distress that required treatment[11]. This symptomatic syndrome is chronic and affects predominantly older women, according to unmodifiable patient-related and disease-related risk factors for TD[12]. In general, for mild to moderate TS, it is recommended to reduce the dose of neuroleptics, switch to atypical medications, or discontinue



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Figure 1 Axial cranial computed tomography without contrast enhancement. A: No lesion within maxillary sinus, pons, and cerebellum; B: No lesion within bilateral basal ganglia; C: No infection sign, such as brain abscesses.

antipsychotic treatment altogether in the hope of promoting remission[13]. Lurasidone, classified as a second-generation antipsychotic, has few adverse side effects pharmacologically related to TS. To date, a 4-patient study has indicated lurasidone as a potential cause of tardive dystonia and tardive akathisia [14]. That the TSS seen in our case was related to lurasidone can be indicated by the temporal relationship. Even though this temporal relationship suggests that our patient's TSS was mainly related to the use of lurasidone, we could not rule out the effects of the previous use of other antipsychotics[13].

CONCLUSION

To our knowledge, this might be the first report to indicate that TSS occurred during lurasidone treatment. It is important that clinicians should adopt a cautious approach when prescribing atypical antipsychotics to prevent the development of TS, although these medications have a lower risk of causing TS.

FOOTNOTES

Author contributions: Lin MC participated in this case report's design and coordination, was involved in data acquisition, and drafted the manuscript; Chang YY participated in both its design and coordination; Lee Y and Wang LJ are co-corresponding authors, they conceived the idea of this case report and its design, and were involved in revising and finalizing the manuscript.

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MINIREVIEWS

Underrecognition and un-dertreatment of stress-related psychiatric disorders in physicians: Determinants, challenges, and the impact of the COVID-19 pandemic

Charles Lung-Cheng Huang

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Abstract

Medical practitioners' duties are highly stressful and performed in a particularly challenging and competitive work environment. Stress and burnout among physicians have emerged as a worldwide public health problem in recent years. A high level of distress and burnout can lead to clinically significant behavioral health problems, such as stress-related psychiatric disorders. Mounting evidence shows that physicians have higher risks of insomnia, anxiety, and depression than the general population, especially during the coronavirus disease 2019 pandemic. However, the behavioral health problems of these vulnerable healthcare professionals are noteworthy for being underrecognized and undertreated. In this mini-review, we summarize the current progress of studies on the prevalence and determinants of distress and stress-related psychiatric disorders among physicians and their healthcare-seeking behaviors. We discuss future research directions and the clinical approach that may maximize self-awareness and promote prompt and adequate treatment for clinically significant behavioral health problems of physicians.

Key Words: Physician; Depression; Anxiety; Insomnia; Healthcare-seeking behavior; Undertreatment

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Core Tip: Physicians are experiencing unprecedented stress and distress. They face major risks of distress and burnout, which can subsequently cause stress-related psychiatric disorders, such as insomnia, anxiety, and depression. Nevertheless, many of these vulnerable healthcare professionals do not seek medical help. There is a clear need for further research to evaluate the determinants of underrecognition and undertreatment of stress-related psychiatric disorders, how to enhance early detection and management of these mental health problems, and how to eliminate obstacles to the use of mental health services in this population.

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INTRODUCTION

Healthcare professionals are well known to bear a heavy burden of high job strain and workplace challenges[1]. High-pressured working environments, with excessive workloads, extended working hours, high levels of time pressure, limited resources, and restricted autonomy, have been acknowledged as factors causing mental health issues of healthcare professionals. In addition to these issues, medical practitioners may also have to deal with medical disputes and hospital evaluations in addition to the challenges of their clinical practice[2]. Distress and burnout, regarded as the exhaustion of emotional or physical strength as a result of prolonged frustration or stress, are common among physicians[3-6]. In a Medscape survey, 56% of physicians said they experienced burnout and attributed it to excessive bureaucracy combined with other causal factors, including long working hours, increasing computerization of practice, lack of respect from colleagues, lack of clinical autonomy, and insufficient compensation[7].

The issue of physicians' wellness has been gaining attention in recent years, and how to measure physicians' wellbeing and mental health is crucial[8]. A lot of literature reports physicians' distress or mental illness in terms of fatigue, burnout, emotional exhaustion or withdrawal, anxiety, depression, suicide, substance abuse, or functioning impairment. Additionally, there are existing instruments that can evaluate physician wellness. For instance, Arnetz[9] used a standardized questionnaire, *i.e.*, the quality of work competence survey, to evaluate core elements of organizational and staff wellbeing. These included mental energy, skills development, work-related exhaustion, work climate, work tempo, leadership, and organizational efficacy.

The high level of occupational stress, distress, and burnout of physicians affects not only their physical and mental well-being, but also the quality of patient care and the overall efficiency and costs of the healthcare system[8,10,11]. Firth-Cozens[11,12] called attention to stress, depression, alcoholism, and suicide among doctors in the United Kingdom in the 1990s. Since then, multiple epidemiological studies and several systematic reviews have been conducted worldwide[13-17]. Their findings are broadly similar as are the causal relationships between rates of stress and stress-related mental disorders, including anxiety, depression, insomnia, and substance use.

The distress, burnout, and subsequent behavioral health problems of healthcare professionals may be aggravated during special circumstances, such as pandemics. For instance, the coronavirus disease 2019 (COVID-19) pandemic has completely altered the lives of millions of people globally, putting an enormous strain on society and healthcare systems[18]. It is anticipated that the mental health problems of healthcare professionals would be exacerbated due to persistent stress and long-term sequelae following COVID-19[19-23].

Doctors' well-being and stress-related behavioral health problems are becoming a global public health issue. However, studies also show that healthcare professionals are passive seekers of help to deal with their mental health problems[24-26]. In this review, we focus on the distress and behavioral health problems of physicians. We extract data from the relevant literature and follow the progress of the latest studies on the prevalence and influential factors of distress and subsequent stress-related psychiatric disorders among physicians. Furthermore, we discuss physicians' healthcare-seeking behaviors and suggest strategies for intervention.

EPIDEMIOLOGY OF STRESS-RELATED PSYCHIATRIC DISORDERS AMONG PHYSICIANS

An increasing body of literature shows that distress and burnout among medical practitioners can lead

to clinically significant behavioral health problems, especially stress-related psychiatric disorders, including depression[15-17,27,28], anxiety[29,30], insomnia[31], substance use[32,33], and even suicide [33-37]. In 2015, a landmark meta-analysis and systematic review analyzed data from 54 cross-sectional and longitudinal studies involving 17560 resident physicians from 18 countries[38]. Results showed that the overall pooled estimate of depression or depressive symptoms was 28.8% [95% confidence interval (CI) = 25.3-32.5]. A review by Yates[3] highlighted that 42% of United States physicians participating in a large-scale online survey in 2018 stated that they experienced burnout. The survey repeated in 2019 showed similar results, with 44% "feeling burned out" and 14% reporting suicidal thoughts. A recent survey of doctors in Hong Kong revealed that 16.0% of the respondents screened positive for depression and 15.3% reported suicidal ideation[28]. In the Canadian Physician Health Study, almost one quarter of physicians reported a period of depression lasting at least two weeks[15], and the rate of depression was higher among female physicians. A study evaluating the levels of an association between occupational stress and depression in Taiwanese physicians found a depression rate (13.3%), which was more than three times higher than that of the general population (3.7%) in Taiwan[16]. The authors also found that gender was not independently correlated with depression, but that the interaction between job control and gender was independent of depression. In a national crosssectional survey of Japanese physicians, depressive symptoms were noted in 8.3% of men and 10.5% of women[37], and 5.7% of men and 5.8% of women exhibited suicidal ideation. Another national study performed before the COVID-19 pandemic revealed that 6.5% of US doctors had suicidal thoughts in the previous year[36]; this rate exceeded the prevalence of suicidal ideation among United States workers in other fields.

Fewer studies have surveyed anxiety disorders in physicians, with early surveys using validated scales suggesting rates of anxiety disorder as high as 24%[39] and post-traumatic stress disorder ranging between 4% and 15%[39,40]. One Canadian study using the posttraumatic stress disorder (PTSD) Checklist-Civilian Version (PCL-C) found a prevalence of probable PTSD of 4.4%[40]. For probable PTSD, no gender differences were observed, but possible PTSD was more common in males (47.3% *vs* 20.4%, $P = 0.001$). Additionally, mean scores were higher for men than for women (30.4 *vs* 25.4, 95%CI = 1.4-8.5, $P = 0.006$). A recent systematic review by Pougnet *et al*[29] found that 7.8%-48.0% of hospital doctors had mood disorders, 2.2%-14.6% had post-traumatic stress disorder, and 10.5%-19.3% had anxiety disorders. In a study of sleep patterns of physicians in Japan, 21.0% of men and 18.1% of women [31] suffered from insomnia.

RISK FACTORS

Several factors are associated with the risks of distress and stress-related psychiatric disorders. Studies investigating the impact of gender on the mental health of physicians found that females were more vulnerable to stress-related psychiatric disorders and suicide[15,37,41,42]. For example, data from the Canadian Physician Health Study indicated that depression was more prevalent among female physicians[15]. Furthermore, more than a quarter of the physicians reported that mental health concerns made it difficult to manage their workload, a problem more common among female physicians. The Norwegian Physicians' Survey indicated that mental health problems were related to low work control (autonomy), time pressure, and demanding patients[24]. There is little gender difference early in the career, but more female doctors than male doctors seem to experience problems in the later years. Schernhammer and Colditz[42] web-based survey showed that female physicians' suicide rate was disproportionately higher than that of male physicians. They reported that the suicide rates of female and male physicians were 2.3 times (95%CI = 1.90-2.73) and 1.4 times (95%CI = 1.21-1.65) higher compared to that of the general population, respectively.

Age and work experience of doctors may also matter[36,41,43]. More experienced and older physicians report lower burnout or psychological distress than younger physicians[43]. This result may due to experienced and older physicians' independence afforded by experience accumulated over time and ever-changing work conditions and the development of protective defenses in their interaction with patients. A study by the British Medical Association revealed that junior physicians reported the highest rate of diagnosis of a mental health condition[41].

Other factors may also contribute to distress and stress-related psychiatric disorders in doctors. For instance, physicians working longer hours seem to be more vulnerable to psychological disturbance [41]. A narrative review found that distress and suicide risks are affected by a lack of positive feedback, emotional exhaustion to the brink of burnout, a lack of support networks, and workplace isolation[44]. Furthermore, risks may be aggravated by long working hours, strained family relationships, and poor work-life balance, as well as organizational and systemic issues. A recent systematic review by Saade *et al*[27] summarized the work-related risk factors of depression, including skill utilization; decision authority; physical and psychological demands; number of hours worked; work schedule (regular/irregular; daytime/nighttime); social support from coworkers, supervisor, and the family; job promotion and recognition; job security; and bullying.

THE IMPACT OF THE COVID-19 PANDEMIC

In several ways, the COVID-19 pandemic has profoundly altered social and occupational environments. There are many factors that influence the mental health of the general population as well as healthcare providers, including fear of infection, social distancing policies, mandatory lockdowns, and isolation periods, as well as suspension of production activity, loss of earnings, and anxiety about the future, together influence the mental health of the general population and healthcare providers. The possibility of high infection rates during the pandemic period added to the stress of healthcare professionals. This included using protective equipment, implementing new medical procedures, long working shifts, staying away from family, *etc*[20].

The distress, burnout, and stress-related psychiatric disorders of medical practitioners seemed to have been exacerbated during the COVID-19 pandemic[20,45-47]. A recent systematic literature review of the symptoms of burnout syndrome in physicians revealed that the overall burnout rate ranged from 14.7% to 90.4% during the outbreak of the COVID-19 pandemic[20]. In addition, the review highlighted that the high prevalence of burnout symptoms was associated with stress, anxiety, and depression; the factors that contributed to burnout included the violent issues related to organizational health as well as the lack of personal protective equipment.

An umbrella review of systematic reviews by Fernandez *et al*[47] found a 17.0%-19.8% rate of anxiety and a 40.4% rate of depression among physicians during the COVID-19 pandemic. In an umbrella review involved 44 meta-analyses[45], 26.7% (95%CI = 19.8-33.6) of hospital doctors reported anxiety and 30.9% (95%CI = 24.9-36.9) reported depression symptoms, while 37.2% (95%CI = 32.61-41.86) suffered from insomnia during the COVID-19 pandemic. In a recent systematic review and meta-analysis by Johns *et al*[46], the pooled prevalence of anxiety and depression was 25.8% (95%CI = 20.4%-31.5%) and 20.5% (95%CI = 16.0%-25.3%), respectively. The authors argued that a significant proportion of physicians experienced high levels of anxiety and depression symptoms during the COVID-19 pandemic, although not conclusively more so than before the pandemic.

A recent study of health professionals' help-seeking behavior during the COVID-19 pandemic in Spain reported a notable increase (29.4%) in the number of referrals to the special clinical unit during the pandemic, especially among physicians compared to nurses[48]. The most prevalent major diagnoses at admission remained similar before and during the pandemic: Adjustment disorders, mood disorders, anxiety disorders, and substance use disorders.

HELP-SEEKING BEHAVIORS AND UNDERTREATMENT OF PHYSICIANS

Although evidence shows that medical practitioners are at high risk of clinically significant behavioral health problems that may require treatment, they tend to be reluctant to seek treatment for mental health problems[25,28,36,41,49]. A recent survey exploring United States doctors' suicidal ideation and attitudes to seeking help found that 1 in 15 doctors reported having suicidal thoughts in the previous 12 mo[36]. Most doctors (72.9%) disclosed that they would seek professional help if they had a serious emotional problem. However, doctors with suicidal ideation were less likely to state that they would seek help (64.2%) than those without suicidal ideation. Earlier research data from the Canadian Medical Association showed that of the 18% of physicians who were recognized as depressed, only a quarter considered seeking help and only 2% actually did[25]. A European study revealed that 78.3% of distressed physicians had never sought professional help for burnout or depression[49]. In a study conducted by the British Medical Association, junior doctors and medical students reported the highest rate of being formally diagnosed with a mental illness, but junior doctors were the least likely to know how to access support or help[41]. A recent survey of physicians in Hong Kong also found that among the cases positive for depression (16.0%), less than half reported having a formally diagnosed mood disorder[28].

Studies using objective data echo the findings of self-report surveys on the help-seeking behaviors of doctors[33,50]. Gold *et al*[33] used data from the National Violent Death Reporting System to explore suicide among United States physicians. They found that although mental illness was a critical comorbidity in doctors who committed suicide, postmortem toxicology testing showed low rates of antidepressants. We also conducted a study using a nationwide population-based database of the National Health Insurance program in Taiwan to explore the actual risk of stress-related psychiatric disorders among healthcare-seeking doctors[50]. A total of 15150 doctors and 45450 matched controls were included, and the results showed that the adjusted odds ratios for treated depression, anxiety, and insomnia in the physicians enrolled were 0.716 (95%CI = 0.630-0.813), 1.103 (95%CI = 1.020-1.193), and 2.028 (95%CI = 1.892-2.175), respectively. In other words, doctors have a higher likelihood of being treated for insomnia and anxiety but a lower likelihood of being treated for depression than the general population. Moreover, we found that undertreatment was more common in female doctors for anxiety; in age groups > 35 years for depression; in surgery and OBS/GYN specialties for anxiety; as well as in surgery and internal specialties for depression.

Doctors' own attitudes may be the reason for their hesitancy in seeking professional help for psychological or behavioral health problems. A survey of United States female physicians revealed that almost 50% believed that they fit the criteria for mental illness although they had not sought treatment[51]. The main reasons for avoiding care included limited time, the belief that diagnosis was embarrassing or shameful, fear of reporting to a medical licensing board, and a belief that they could independently manage their illness. A recent study of Australian physicians' help-seeking for depression found that the most common barrier to help-seeking was "confidentiality/privacy"[52]. In addition to the fear of professional consequences, *e.g.*, the impact on the medical license[53], physicians identified barriers such as limited time to seek medical treatment and the stigma attached to mental illness[54]. Previous studies have suggested that physicians are reluctant to see another professional, especially if the problem is psychological[26,55]. Doctors become used to coping with their distress or psychological problem through avoidance and denial, although the effect is doubtful[11,56,57]. Instead, most doctors tend to use self-prescribed medications and self-treatment for their own psychological distress or medical illness[24,49,58,59].

Doctors' attitudes can hinder their access to proper health care for themselves. Physicians are not used to the role of being the patient and fear that their need for help may be seen as a mark of their inability to cope or weakness[55,60,61]. Such a perceived stigma is associated with resistance to help-seeking. In an anonymous survey of 1401 academic physicians in the United States, 12% reported moderate to severe depressive symptoms in the previous two weeks[62], but of these, less than half reported that they were likely to seek treatment for a mental health problem. More than half the doctors endorsed survey items about the stigma attached to mental illness. It is worth noting that the fear of being stigmatized can develop as early as when the doctors are students[63-65]. In a survey of students at six medical schools in the United States, only a third of the respondents with burnout sought help for a mental health issue in the last 12 mo[63]. The authors concluded that negative personal experiences, perceived stigma, and the hidden curriculum may lead to the majority of students not seeking the help they needed.

RECOMMENDED MANAGEMENT AND INTERVENTION STRATEGIES

As physicians' mental health problems have been globally recognized as a health crisis, an increasing number of researchers have proposed action plans and intervention strategies in recent years, although not all of them are validated. Interventions to deal with this problem can be divided into two categories: Those focusing on the individual; and those addressing the work environment[3,66]. Individual-focused programs frequently comprise instruction in mindfulness, exercise, and nutrition, while programs on dealing with the work environment focus mainly on stressors such as productivity pressures, electronic health records, and the administrative burden.

In a recent review focusing on physician stress and burnout, Yates[3] proposed a number of solutions, including decreasing the amount of time physicians spend on non-clinical tasks, organizational changes to improve usability of electronic medical record systems, the adoption of scribes, personal resilience methods focused on self-care, and programmatic approaches to promoting physician well-being. Other authors also recommend specific interventions such as meditation, mindfulness training, and individualized professional coaching and groups for stress management[67-70]. Posluns and Gall[68] focused on the role of self-care in promoting well-being and suggested self-care practices including awareness, balance, flexibility, social support, physical health, and spirituality. Furthermore, they suggested integrating self-care practice into clinical training programs and the quality assurance courses of professional associations in the field of mental health.

A number of interventions have been established to improve the well-being of junior physicians and resident doctors[71-74]. For example, a recent study assessed an educational program, the Resident Physician Burnout and Peer Communication Curriculum, aimed at promoting a strong informational and emotional social support system[73]. The course used peer roleplaying to establish self-awareness and social support, enhance communication skills, and inform about available mental health resources, thus encouraging intervention. The author concluded that roleplaying provided an effective, low-cost method of destigmatizing *via* encouraging discussion of burnout, educating about signs and symptoms, and learning about available resources. In their recent review, Krishnan *et al*[71] identified three main types of interventions in the United Kingdom: Mentorship, clinical preparation interventions, and mindfulness. Most of the studies reviewed showed positive outcomes of interventions, suggesting them to be advantageous in reducing stress levels and anxiety, and thereby improving the well-being of young doctors. However, a study evaluating a suicide screening and treatment referral program for faculty and residents at an academic medical center in the United States highlighted the challenges of engaging the professionals in the program, although the minority who successfully participated in the treatment referral program were satisfied with the outcomes[74].

Medical residents and doctors often find it inconvenient to receive professional counseling owing to concerns about cost, time, confidentiality, and stigma. The distress and mental health problems of frontline physicians exacerbated by the COVID-19 pandemic emphasize the need for accessible psycho-

Table 1 Summary of recommended management and intervention strategies

Individual	Work environment	Program	Ref.
Personal resilience methods focused on self-care	Decreasing the amount of time physicians spend on non-clinical tasks, organizational changes to improve usability of electronic medical record systems, the adoption of scribes	Programmatic approaches to promoting physician well-being	[3]
Meditation, mindfulness training, and individualized professional coaching and groups for stress management			[67-70]
Self-care practices including awareness, balance, flexibility, social support, physical health, and spirituality		Integrating self-care practice into clinical training programs and the quality assurance courses of professional associations	[68]
Peer roleplaying to establish self-awareness and social support, enhance communication skills, and inform about available mental health resources, thus encouraging intervention	A strong informational and emotional social support system	Resident physician burnout and peer communication curriculum	[73]
Mindfulness	Mentorship	Clinical preparation interventions	[71]
	Providing confidential, free, and individual on-site counseling and medication management	RFWP	[76]
	A novel smartphone app offering a digital-first mental health resource		[75]
Normalizing depression as a medical disorder, decreasing the stigma of mental disorders, and encouraging faculty and physicians to seek treatment			[72]

RFWP: Resident and Faculty Wellness and Peer Support Program.

logical support for medical professionals. There are novel approaches to reducing barriers[75,76]. For instance, the Resident and Faculty Wellness and Peer Support Program at Oregon Health and Science University has sought to reduce these obstacles by providing confidential, free, and individual on-site counseling and medication management[76]. During the COVID-19 pandemic, all appointments *via* this program were shifted to a telehealth service and many doctors were grateful for the opportunity to talk through their apprehensions and strengthen their coping ability. Another study investigated a novel smartphone app offering a digital-first mental health resource to young physicians[75]. It contained psychoeducational material, information on common work stressors, cognitive behavioral modules, guided meditation, and a section on help-seeking options for mental health problems through workplace and private routes. Results showed that anxiety and depressive symptoms significantly decreased between the pre- and post-assessment points; however, doctors' safety concerns about COVID-19 significantly increased.

In a special article aiming to reduce the stigma associated with mental illness and encourage medical students to seek treatment, Brower[72] suggested that faculty attitudes toward mental health problems, including unwillingness to acknowledge having such issues, may be transmitted to medical students educated by them and keep depression concealed *via* the hidden curriculum. In addition, the fear of mental illness is manifested as privileging applications and licensing under the guise of patient safety, leading to a culture of shame and silence. Brower[72] appealed to medical faculty and physicians, as founders and executors of this professional culture, to be the ones to start changing it. The article also provides suggestions for normalizing depression as a medical disorder, decreasing the stigma of mental disorders, and encouraging faculty and physicians to seek treatment (Table 1).

CONCLUSION

Healthcare providers' mental wellness has become a worldwide public health concern. The literature on stress-related mental health conditions of these vulnerable professionals and their determinants was limited until a few years ago. Although recent research has begun to focus on action plans and intervention strategies, few mention the barriers to help-seeking and the impacts of doctors' mental health problems on patient care[77]. The present review highlights that physicians have high risks of distress, burnout, and subsequent stress-related psychiatric disorders, which may be further exacerbated during the COVID-19 pandemic. However, at-risk physicians are still notably underrecognized and undertreated. Doctors' reluctance to seek help may be largely due to their own attitudes,

especially the stigma attached to mental illness. Our review is limited by its focus on qualitative analysis without quantitative analyses, such as the effectiveness of mental health interventions in doctors.

We hope that this review encourages a number of future considerations. Firstly, improved awareness of the significance of physician wellness, both organizationally and individually, is needed by physicians, their employers, and their patients. Inclusion of physician wellness as an indicator of quality of organizations might be the first step that can lead to a shift in the culture of care for physicians' wellness. Thus, health systems and organizations should routinely measure physician wellness and the level of distress and burnout, establish evidence-based intervention strategies, and discuss the challenges related to their implementation. Secondly, educating physicians themselves, especially medical students and future doctors, about the impact of mental health problems, how to develop self-awareness and help-seeking, and how to eliminate the stigma is crucial. Finally, more prospective and longitudinal studies are needed to explore the causes, manifestations, impacts, and determinants of distress, burnout, and subsequent stress-related psychiatric disorders in physicians. Moreover, research on health care-seeking behaviors of physicians, as well as the possible barriers, both individual and organizational, to their use of mental healthcare resources is necessary. Accordingly, assessment of comprehensive management and novel intervention methods, such as telehealth, digital medicine, groups, and other outreach treatments, and their efficacy is also highly recommended.

FOOTNOTES

Author contributions: Huang CLC designed the research study, performed the research, wrote the manuscript, and approve the final manuscript.

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MINIREVIEWS

Kynurenine pathway of tryptophan metabolism in pathophysiology and therapy of major depressive disorder

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Abstract

Serotonin deficiency in major depressive disorder (MDD) has formed the basis of antidepressant drug development and was originally attributed to induction of the major tryptophan (Trp)-degrading enzyme, liver Trp 2,3-dioxygenase (TDO), by cortisol, leading to decreased Trp availability to the brain for serotonin synthesis. Subsequently, the serotonin deficiency was proposed to involve induction of the extrahepatic Trp-degrading enzyme indoleamine 2,3-dioxygenase (IDO) by proinflammatory cytokines, with inflammation being the underlying cause. Recent evidence, however, challenges this latter concept, as not all MDD patients are immune-activated and, when present, inflammation is mild and/or transient. A wide range of antidepressant drugs inhibit the activity of liver TDO and bind specifically to the enzyme, but not to IDO. IDO induction is not a major event in MDD, but, when it occurs, its metabolic consequences may be masked and overridden by upregulation of kynurenine monooxygenase (KMO), the gateway to production of modulators of immune and neuronal functions. KMO appears to be activated in MDD by certain proinflammatory cytokines and antidepressants with anti-inflammatory properties may block this activation. We demonstrate the ability of the antidepressant ketamine to dock (bind) to KMO. The pathophysiology of MDD may be underpinned by both the serotonin deficiency and glutamatergic activation mediated respectively by TDO induction and N-methyl-D-aspartate receptor activation. Inhibition of TDO and KMO should be the focus of MDD pharmacotherapy.

Key Words: Major depressive disorder; Indoleamine 2,3-dioxygenase; Kynurenine monooxygenase; Proinflammatory cytokines; Serotonin deficiency; Tryptophan 2,3-dioxygenase

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Core Tip: Antidepressant drugs inhibit the activity of liver tryptophan 2,3-dioxygenase (TDO) and bind specifically to the enzyme, but not to indoleamine 2,3-dioxygenase (IDO). IDO induction is not a major event in the pathophysiology of major depressive disorder (MDD), but may be masked and overridden by upregulation of kynurenine monooxygenase (KMO), the gateway to production of modulators of immune and neuronal functions. The pathophysiology of MDD may be underpinned by both the serotonin deficiency and glutamatergic activation mediated respectively by TDO induction and N-methyl-D-aspartate receptor activation. Inhibition of TDO and KMO should be the focus of MDD pharmacotherapy.

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INTRODUCTION

Serotonin deficiency in major depressive disorder

Antidepressant drug development has been based on the monoamine hypothesis of affective disorders that postulates a deficiency of one or more monoamines and the need to develop agents that can inhibit either their breakdown (monoamine oxidase inhibitors) or their reuptake and subsequent degradation [tricyclic antidepressants (TCAs), serotonin-specific and serotonin-noradrenaline reuptake inhibitors]. The serotonin deficiency was originally suggested from observations by Curzon and Bridges[1] that patients with depression exhibit raised cortisol levels that can induce the synthesis of liver tryptophan 2,3-dioxygenase (TDO; formerly Trp pyrrolase) resulting in accelerated peripheral Trp degradation and hence a decrease in its availability to the brain for 5-HT synthesis. Brain (Trp) is the major determinant of 5-HT synthesis, because Trp hydroxylase exists partially (≤ 50%) saturated with its Trp substrate[2]. Depriving the brain of Trp by the acute Trp depletion test reverses antidepressant-induced remission in depressed patients[3].

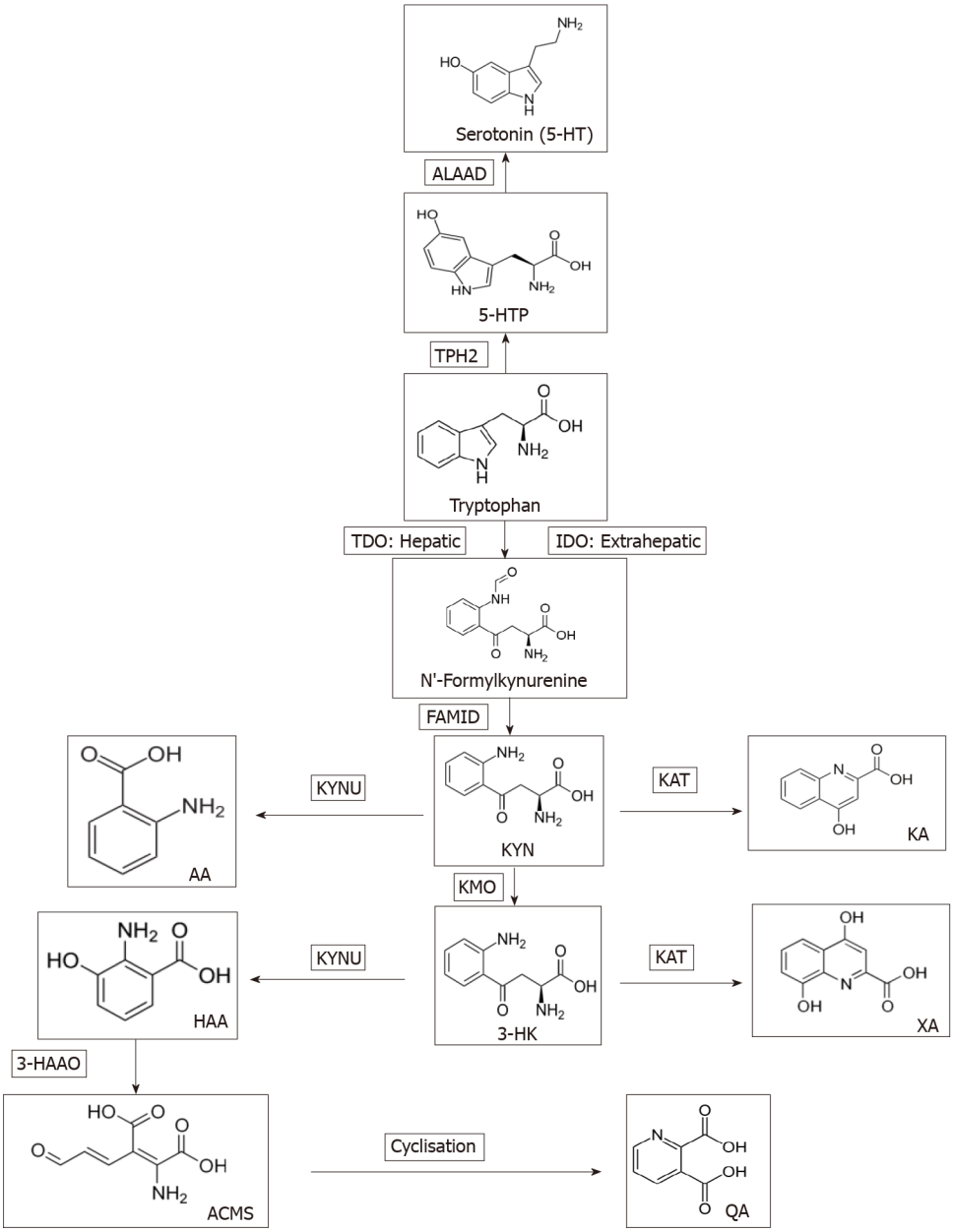
Inhibition of liver TDO by antidepressant drugs

Curzon[4] suggested that TDO is a biochemical factor in depressive illness and Samsonova and Lapin were the first to demonstrate TDO inhibition by some TCAs[5]. Subsequently, a wide range of antidepressant drugs of various structures and pharmacological profiles were shown to inhibit TDO activity in rat liver *in vitro* and after administration[6-13]. TDO inhibition occurs with doses as small as 0.5 mg/kg body weight[7] and involves prevention of conjugation of the inactive apoenzyme with its heme activator and cofactor. TDO inhibition by antidepressants therefore depends on extent of the heme saturation of the apoenzyme and also of its glucocorticoid induction by cortisol, with some antidepressants being better inhibitors of heme-activated TDO, whereas others are better inhibitors of cortisol-induced TDO[13]. Ability of antidepressants to lower raised cortisol levels is another determinant of TDO inhibition[13].

Further evidence of the targeting of TDO by antidepressant drugs was provided by our group, using molecular docking *in silico*: A technique for screening potential inhibitors of target proteins[14,15], but is also useful to confirm known inhibitors. We demonstrated high docking scores (strong binding) of many antidepressants, including amoxapine, citalopram, fluoxetine, fluvoxamine, moclobemide, paroxetine, seproxetine, sertraline[16], tianeptine and venlafaxine, but not the non-antidepressant drugs pargyline and mefenamic acid[17] to the crystal structure of TDO, but no docking to that of the extrahepatic IDO. Thus, antidepressants target TDO and this could explain their ability to restore serotonin homeostasis, at least in part, by reversing the defective serotonin synthesis. As TDO is the first and rate-limiting enzyme of the kynurenine (Kyn) pathway (KP), a description of this pathway and its intermediates may be useful at this point (Figure 1).

The KP of Trp metabolism

The KP is the major pathway of Trp degradation, accounting for 95% of dietary Trp metabolism, with the hepatic pathway contributing 90% and the extrahepatic pathway the remaining 5%, though contribution of the latter pathway is significantly increased by immune activation of IDO by interferons and other proinflammatory cytokines[18]. The liver contains all the enzymes leading to NAD^+ synthesis, whereas other tissues express fewer enzymes[18]. Production of Trp metabolites in extrahepatic tissues including immune cells will therefore depend on the enzymes present. In the absence of TDO or IDO induction, the Kyn produced in liver or IDO-containing tissues can be transported elsewhere for further



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Figure 1 Tryptophan metabolism to serotonin and kynurenine metabolites. AA: Anthranilic acid; ALAAD: Aromatic L-amino acid decarboxylase; ACMS: 2-amino-3-carboxymuconic acid-6-semialdehyde; FAMID: N-formylkynurenine formamidase; 3-HAA: 3-hydroxyanthranilic acid; 3HAAO: 3-hydroxyanthranilic acid 3,4-dioxygenase; 3-HK: 3-hydroxykynurenine; 5-HT: 5-hydroxytryptamine (serotonin); 5-HTP: 5-hydroxytryptophan; IDO: Indoleamine 2,3-dioxygenase; KA: Kynurenic acid; Kyn: Kynurenine; KAT: Kynurenine aminotransferase; KYNU: Kynureninase; KMO: Kynurenine monooxygenase (Kyn hydroxylase); NFK: N-formylkynurenine; QA: Quinolinic acid; Trp: Tryptophan; TDO: Tryptophan 2,3-dioxygenase; XA: Xanthurenic acid; TPH2: Tryptophan hydroxylase isoform 2.

metabolism. Activity of the KP controls plasma Trp availability for cerebral serotonin synthesis and results in production of a range of Kyn metabolites that influence immune and neuronal functions[18].

Control of plasma Trp availability

Control of plasma Trp availability to tissues including the brain is primarily the function of liver TDO. Thus, deletion of the *tdo2* gene in mice increases plasma (Trp) by up to 12.7-fold[19,20] and brain (Trp) by 10.6-fold[21]. The increase in brain (Trp) is associated in increased 5-HT synthesis[21]. By contrast, deletion of the *IDO1* or *IDO2* gene does not alter Trp availability to the brain or 5-HT synthesis[21]. Trp availability for cerebral 5-HT synthesis is therefore determined by hepatic TDO activity in the first place, but also, secondarily, but more immediately, by 2 other determinants: albumin binding of plasma Trp and extent of competition for entry into the brain from a group of large neutral or competing amino acids (CAA), mainly Val Leu, Ile, Phe and Tyr. The best predictor of likely change in brain Trp and hence 5-HT synthesis is the ratio in plasma of Trp/CAA[13]. Plasma Trp exists largely (90%-95%) bound to albumin, with 5%-10% being freely available for tissue uptake. Binding is determined by levels of

albumin and of the physiological displacers of bound Trp, nonesterified fatty acids (NEFAs). Free Trp can therefore be easily altered by dietary, hormonal and pharmacological factors that influence Trp binding[22]. Under certain conditions wherein displacement of bound Trp is strong and sustained, the rise in free Trp will be associated with a decrease in total Trp, due to the rapid equilibration between the free and total fractions. Investigators should be careful in interpreting the changes in Trp disposition under these conditions[22], and whereas most investigators measure the ratio of total Trp/CAA, the ratio of free Trp/CAA is a more accurate measure in situations other than after acute Trp depletion or loading, as these are associated with parallel changes in both free and total Trp.

Neuronal and immune properties of KP metabolites

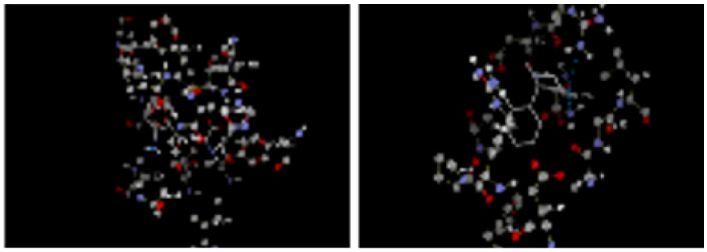
Neuronal activity is influenced by the cytoprotective kynurenic acid (KA) and excitotoxic quinolinic acid (QA) as antagonist and agonist respectively of the N-methyl-D-aspartate (NMDA) receptors of the excitatory amino acid glutamate[23], with the balance between QA and KA determining the level of neuronal excitability. Immune function is influenced by several Kyn metabolites. 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA) and QA are the main proinflammatory metabolites that undermine T-cell function[18], whereas picolinic acid (PA) is anti-inflammatory. KA is dually acting [24]. KMO is the gateway for production of these metabolites and the pathway favours Kyn oxidation by KMO to 3-HK and hydrolysis of the latter to 3-HAA by KYNU, because of the relatively high affinity of both enzymes towards their respective substrates[18]. 3-HAA 3,4-dioxygenase is the most active of KP enzymes, hence the rapid conversion of 3-HAA to an unstable intermediate that cyclises non-enzymically to QA[18]. Affinity of Kyn aminotransferase (KAT) towards its Kyn and 3-HK substrates is much weaker, hence the relatively low production of KA and xanthurenic acid, formation of both of which requires increased levels of the KAT substrates[18]. KMO gene deletion in mice decreases plasma 3-HK and QA by about 86% and 92% respectively and increases concentrations of Kyn, KA and AA by 15-, 133- and 4-fold respectively[25]. Thus, KMO inhibition diverts Kyn metabolism towards the cytoprotective KA. By contrast, activation of KMO can enhance the conversion of Kyn to 3-HK leading to decreased Kyn levels: An effect that will neutralise the rise in Kyn expected with TDO and/or IDO induction. This may explain the frequent observation that the reported increase in the Kyn/Trp ratio after mild immune activation is mostly due to the decrease in Trp, rather than an increase in Kyn[26]. These aspects may help explain some of the KP changes in MDD and their modulation by antidepressants (see below). Investigators use the plasma Kyn/Trp ratio to express indirectly IDO activity. While this may apply correctly in *in vitro* culture or cell systems, this ratio is not specific for IDO in *in vivo* situations, as other factors also alter it, including TDO activity, flux of plasma free Trp down the KP and activities of KMO and KYNU[26].

Inflammation and glutamatergic activity in major depressive disorder

The involvement of inflammation in major depressive disorder (MDD) was first proposed following the observation[27] that hepatitis C patients treated with interferon-alpha (IFN-α) become depressed. As this cytokine is an IDO inducer, the concept that serotonin deficiency in MDD is underpinned by IDO induction secondarily to inflammation was born. Extrapolating from hepatitis C to MDD was however unwise, given that Trp metabolism is already compromised by this virus and the use of IFN-α can only potentiate the effect of the virus on Trp metabolism, in particular IDO induction[17]. Although many studies of the immune status in MDD followed, recent studies suggested that not all MDD patients are immune-activated and, when present, inflammation is mild and/or transient and its reversal does not reflect clinical outcome[28,29]. Elevation of proinflammatory cytokines in some patients is not associated with an inflamed subgroup, but is due to a right shift of the immune marker distribution[30]. In MDD, reports of changes in the Kyn/Trp ratio used to express IDO activity are contradictory, partly because of the non-specificity of this ratio[26]. Whereas considerable evidence exists for liver TDO inhibition leading to elevation of plasma and brain Trp and enhanced serotonin synthesis in rats by a broad range of antidepressant drugs[6-8], and emerging evidence for inhibition of the accelerated Trp degradation in MDD by escitalopram causing an increase in plasma Trp[31], little is known about potential IDO inhibition by antidepressants. The absence of docking of antidepressants to IDO[17] suggests that this extrahepatic enzyme does not play a role in MDD antidepressant therapy and this notion is supported by the observations that the Kyn/Trp ratio does not link inflammation with depressive symptoms[32], and that IDO expression in monocytes of MDD patients is not different from that in healthy controls[33], though this may reflect patient heterogeneity.

Antidepressants and KP enzymes

As stated above, antidepressant drugs inhibit and target liver TDO, but not extrahepatic IDO[17]. Even when IDO is induced in some MDD patients by proinflammatory cytokines, it is most likely that the effect of this induction (as well as that of TDO) will be masked, superseded or overridden by changes in subsequent KP enzymes, notably KMO. KMO activation in MDD is gaining ground and may be another important biochemical event in the pathophysiology of this disorder. KMO activation can result in decreased levels of the Kyn substrate and consequently in the Kyn transamination product KA, as has been reported in unmedicated MDD patients[34,35]. While many antidepressants have previously been



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Figure 2 Molecular docking of kynurenine and ketamine to kynurenine monooxygenase. Docking was performed using the Molegro virtual Docker software as described previously[16,17], but with kynurenine monooxygenase. With kynurenine (top), the best scored docking solution of 5y66 with the reference ligand, amino acids in the active site are presented in ball and stick with element colour and ligand is presented in thick lines with element colour (where carbon is grey, oxygen is red, nitrogen is blue, sulphur is yellow and hydrogen is white). Blue lines represent the hydrogen bonds in between the ligand and the active site of 5y66. Docking parameters were as follows: Kynurenine: Molecular weight (207.206), docking score (-95.4662), re-rank score (-81.6652), root mean square deviation (RMSD) (2.19513), torsion (4), H-bond (-6.03152). Amino acid residues at the kynurenine monooxygenase (KMO) active site are: Gly321, Ile224, Phe319, Met373, His320, Ala56, Leu226, Phe319, ligand binding amino acid residues are: Tyr404, His320, and Leu226. With ketamine (bottom), molecular weight (237.725), docking score (-81.8059), re-rank score (-65.0284), RMSD (zero), torsion (2), H-bond (-0.0342033). Amino acid residues at the KMO active site are: Asp112, Arg39, Gly16, Ala15, Glu37, Phe131, Arg111, Arg100, ligand binding amino acid residues are: Asn 115, Arg111. KMO: Kynurenine monooxygenase; KYN: Kynurenine.

proposed to act by reducing inflammation and hence inhibition of IDO induction, it is more likely that they act by inhibiting KMO activation by cytokines, notably, interleukin-1β and IFN-γ[36], as has been demonstrated with ketamine[29], escitalopram[31] and sertraline[37]. Additionally, whereas ketamine does not dock to either TDO or IDO and so is unlikely to inhibit either enzyme[17], we demonstrate here for the first time its strong docking to KMO (Figure 2), that is comparable with that of the reference ligand Kyn itself, and suggest that KMO inhibition is likely to be one mechanism of action of ketamine.

The role of anti-inflammatory drugs in MDD therapy

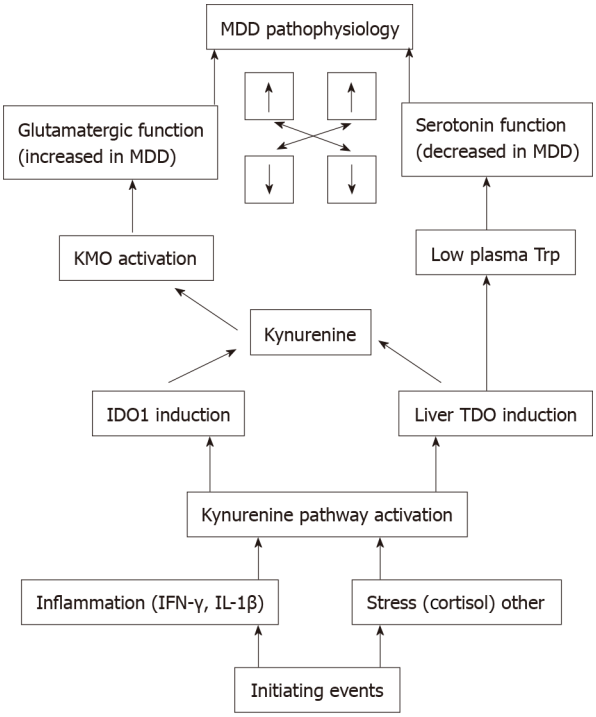
Current evidence suggests that anti-inflammatory strategies have not met with the anticipated success in MDD therapy and that only MDD patients with chronic inflammation may benefit from such therapy, while other patients with low-grade inflammation may experience harm[38]. Of 6 non-steroidal anti-inflammatory drugs tested, only salicylic acid (the active aspirin metabolite) docks to TDO[17] and aspirin appears to be an effective single or adjunctive therapy of MDD if given in relatively small doses and for short- to medium-term durations, but not for long-term use, which does not protect against depression and can actually induce it[18]. Mechanisms of these opposite effects of aspirin involve modulation by salicylate of Trp metabolism and disposition in opposite direction[17].

Serotonin and glutamate interactions

KMO activation leads to production of the excitotoxic Kyn metabolite and NMDA receptor agonist QA. Glutamatergic activity can therefore be enhanced in at least some MDD patients. Mutual interactions between serotonergic and glutamatergic activities are well established and may be important determinants of MDD pathophysiology. Thus, serotonin modulates glutamate neurotransmission in several brain regions, especially those involved in cognition, motor function and nociception, with raphe neurons being immune-positive for glutamate[39]. The cognitive and emotional disorders in MDD due to defective serotonin function can in part be due to disruption of the serotonin control over glutamate and gamma-aminobutyric acid neurotransmission[40,41]. On the other hand, NMDA receptors may regulate behavior by modulating serotonin and dopamine function[42,43]. Though complex in nature, this mutual interaction can be viewed simplistically as low serotonin losing control over glutamate neurotransmission and inhibition of the latter facilitating serotonin function (Figure 3).

CONCLUSION

We hypothesized that the KP is at the center of MDD pathophysiology and a target of antidepressant therapy. Figure 3 outlines the potential role of the KP in MDD and emphasizes the importance of TDO and KMO, the inhibition of which is likely to become the focus of pharmacotherapy of MDD. Studies on the frequency of KMO enhancement and its mechanism(s) in MDD are needed. Effects of antidepressants other than ketamine and escitalopram on enzymes and metabolites of the KP should be investigated. KMO inhibition therapy could be explored in MDD. We suggest that lowering glutamatergic activity by KMO inhibition can restore serotonin function and should be recognized as a new mechanism of antidepressant action, perhaps exemplified by ketamine. The rapid and novel mode of action of ketamine should encourage the search for safer and longer-acting alternatives. The requirement of normal serotonin levels in the antidepressant-like efficacy of ketamine in rodent models



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Figure 3 Schematic representation of the proposed role of the kynurenine pathway in the pathophysiology of major depressive disorder. Mutual interactions between serotonergic and glutamatergic functions are indicated by the bidirectional arrows for increased or decreased function. MDD: Major depressive disorder; KMO: Kynurenine monooxygenase; Trp: Tryptophan; IDO: Indoleamine 2,3-dioxygenase; TDO: Tryptophan 2,3-dioxygenase; IFN: Interferon; IL: Interleukin.

[44] may explain in part the transient efficacy of the drug in humans. Furthermore, studies with the two ketamine enantiomers suggest that NMDA receptor antagonism is not the sole mechanism of the drug's antidepressant action[45]. KMO inhibition and blockade of progress of the KP to QA formation is thus far a potential mechanism of ketamine action. Addressing the above issues may provide a way forward in the search for the ideal MDD pharmacotherapy.

FOOTNOTES

Author contributions: Badawy AAB wrote the first draft; Dawood S and Bano S reviewed it and all three authors approved the final version.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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MINIREVIEWS

Reducing psychiatric illness in the perinatal period: A review and commentary

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Abstract

This brief overview highlights the global crisis of perinatal psychiatric illness (PPI). PPI is a major contributor to many adverse pregnancy, childbirth, and childhood development outcomes. It contributes to billions of dollars in spending worldwide each year and has a significant impact on the individual, their family, and their community. It is also highly preventable. Current recommendations for intervention and management of PPI are limited and vary considerably from country to country. Furthermore, there are several significant challenges associated with implementation of these recommendations. These challenges are magnified in number and consequence among women of color and/or minority populations, who experience persistent and negative health disparities during pregnancy and the postpartum period. This paper aims to provide a broad overview of the current state of recommendations and implementation challenges for PPI and layout a framework for overcoming these challenges. An equity-informed model of care that provides universal intervention for pregnant women may be one solution to address the preventable consequences of PPI on child and maternal health. Uniquely, this model emphasizes the importance of managing and eliminating known barriers to traditional health care models. Culturally and contextually specific challenges must be overcome to fully realize the impact of improved management of PPI.

Key Words: Perinatal psychiatric illness; Postpartum depression; Equity-oriented care; Minority populations; Maternal mortality; Pregnancy

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Core Tip: Perinatal psychiatric illness is a major contributor to maternal mortality and morbidity rates, especially among women of color. This paper explores the ways in which current standard of practice is failing to address these disparities and offers an alternative framework for consideration.

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INTRODUCTION

Rates of maternal morbidity and mortality are a global health crisis. In 2017, 295000 women worldwide perished due to maternal causes[1]. Global maternal mortality rates are estimated at 211 maternal deaths per 100000 live births. The lifetime risk of maternal mortality for a 15-year-old girl is estimated at 1 in 190[1]. Mortality rates are more than 40 times higher in underdeveloped countries compared to developed geographic areas such as Europe and Australia[1]. There are major differences in rates of maternal mortality and morbidity. Differences can be seen between countries, with sub-Saharan Africa and Southern Asia accounting for approximately 86% of all estimated global maternal deaths in 2017[1]. Differences based on minority status can also be seen within countries. In the United States, Black women are 2.5 times more likely to die in childbirth than White women[2]. In the United Kingdom, Black and Asian women are more likely to die of maternal-related causes than White women[3]. Ethnic minorities (*e.g.*, non-Han women) in China have higher maternal mortality rates than non-minority populations (*e.g.*, Han women[4]). In Brazil, non-white women are 3.5 times more likely to die from obstetric deaths than White women[5]. In Australia, Indigenous women have a maternal mortality rate 4.6 times higher than non-Indigenous women[6]. These trends are consistent worldwide.

Maternal Mortality Review Committees have determined that 11% of pregnancy-related deaths are due to perinatal psychiatric illness (PPI), and these deaths are 100% preventable[7]. PPI is the most common morbidity in pregnancy and the leading cause of mortality during the perinatal period in developed nations[8]. PPI is a significant contributor to poor outcomes throughout pregnancy, childbirth, and postpartum. Rates of PPI in high-income countries range from 7%-15%, while the prevalence ranges from 19%-25% in low- and middle-income countries[9]. Women of color are especially at risk for PPI. In the United States, Black, Asian/Pacific Islander and Hispanic/Latinx women report experiencing PPI at 2-5 times the rates of White women[10,11]. In the United Kingdom, non-White (especially Asian) women experience PPI at higher rates than White women[12]. In Norway, the prevalence of PPI in women of underrepresented ethnicities was almost 3 times that of Western Europeans[13]. Research on racial disparities is limited. Many studies combine all racial and/or ethnic minorities together, which disregards important differences between races and cultures.

PPI refers to any psychiatric illness experienced from the beginning of pregnancy up to 1 year postpartum. A landmark study of 10000 mothers found that of women who screened positive for depression, 27% reported being depressed before pregnancy and 33% reported that their depression began during pregnancy[14]. Though many primarily think of postpartum depression when referring to PPI, there are several psychiatric illnesses that are prevalent and related to negative outcomes during the perinatal period. Perinatal depression is indeed common, occurring in around 25% of women[15]. It refers to the occurrence of a major depressive episode in the perinatal period, marked by low mood, low energy, sleep problems (apart from caring for the infant), and sometimes suicidal thoughts. This is differentiated from what has been called the "baby blues" or the "maternity blues", which refers to a transient affective disturbance that usually peaks within 5 d after childbirth[16]. PPI also refers to psychiatric symptoms beyond depression. Perinatal anxiety presents with symptoms such as excessive and uncontrollable worries about the baby and motherhood, fear of childbirth, and intrusive thoughts of the baby being harmed or dying[17]. It may occur at higher rates than perinatal depression[18]. Perinatal obsessive-compulsive disorder is more common than obsessive-compulsive disorder in the general population and is marked by obsessions and compulsions related to the baby[19]. Obsessions are generally related to fears of contamination and harming the baby and compulsions may include avoidance of child-rearing tasks and mental rituals[19]. Perinatal post-traumatic stress disorder (PTSD) refers either to a recurrence of PTSD brought on by major life changes during pregnancy and postpartum or to new onset PTSD secondary to traumas experienced during pregnancy or childbirth. Symptoms include nightmares, avoidance of stimuli associated with the trauma, and negative

appraisals of self and others related to the trauma[20]. Finally, perinatal psychosis, though relatively rare, is an emergent situation. It typically occurs within 2-3 d of childbirth, though emerging evidence suggests that some women may even experience it prenatally. It is most common in women with a history of bipolar disorder or with a first-degree relative with schizophrenia or bipolar disorder[21].

PPI is associated with a range of negative outcomes. Women experiencing PPI tend to initiate prenatal care later and miss more appointments. Both factors are highly associated with poor childbirth outcomes[22-24] and are targets for appropriate intervention like psychoeducation and enhanced awareness of PPI. PPI is also associated with pregnancy and delivery complications (such as high blood pressure, gestational diabetes premature labor, low infant APGAR score, low birth weight[25]). Specific findings stratifying risk by ethnicity and race are limited. One United States study found that non-Hispanic Black and Asian women have higher levels of risk for preterm birth while depressed than White women, and Hispanic women were not at higher risk for preterm birth when depressed[26].

Women with PPI and their babies also experience postpartum comorbidities associated with psychiatric illness. Women with PPI have more trouble bonding with their baby, and mental health concerns can be seen 4-5 years postpartum in 30%-40% of women[22,27,28]. The children of women with untreated psychiatric distress go on to have higher rates of psychiatric illness, behavioral problems, and academic difficulties[29]. To illustrate, a French study showed increased externalizing and internalizing behavior and poor motor and regulation skills in 1-year-old children of mother with perinatal depression[30]. These findings were replicated in a large (n = 2698) study out of the Netherlands examining internalizing behavior in 3-year-old children of women with perinatal anxiety and depression[31]. Studies of teenagers (aged 16 to 17-years-old) in Finland and the United Kingdom demonstrated increased risk for depression and low social competence when their mother had experienced perinatal depression[32,33].

Risk factors for PPI are myriad and many are quite common. Individual risk factors include unwanted pregnancy (50% of pregnancies), primiparity (*i.e.*, first pregnancy), and fertility difficulties [34]. Social determinants of health related to PPI include childhood maltreatment, especially childhood sexual violence, which affects up to 25% of girls from low-income and middle-income countries[9]. Other social determinants that increase risk for PPI and are disproportionately experienced by women of color and underrepresented ethnicities are poverty, poor nutrition, lower levels of educational attainment, low social support, gender discrimination and gender-based violence, and previous mental health conditions[9,34,35]. Again, studies stratifying risk for PPI by race and ethnicity are extremely limited, though there is evidence for the deleterious impact of immigration and race-based discrimination on mental health (*i.e.*, increased risk for PPI) in the perinatal period[36]. Adversity more commonly observed in underrepresented populations, such as intimate partner violence, childhood trauma and military deployment, is also associated with greater risk for mental health outcomes[36].

Untreated PPI can have devastating consequences for mothers, their partners, their children, their workplaces, and their communities. At the population level, PPI is associated with increased healthcare costs, inappropriate use of healthcare (*i.e.*, excess- and under-utilization as well as increased use of emergent care), child abuse, family dysfunction, and, at worst, suicide, homicide, and infanticide[22,37]. At the individual level, PPI impacts the mother's health, attachment with their child, the infant's health, and can lead to suicide or homicide[38,39]. At an economic level, the cost of PPI is significant. Though research on exact costs worldwide are limited, studies out of Canada and South Africa suggest that women with PPI utilize services costing roughly 2 times those of women without PPI[40,41]. In the United States, PPI costs an estimated $14 billion per year, including cost estimates of loss of productivity and direct healthcare[42]. Even when strictly examining medical costs in the United States, PPI costs 5 times as much as other pregnancy concerns like gestational diabetes or postpartum hemorrhage[43].

Given the regular touchpoints between pregnant women and providers during the prenatal period and the onset of many psychiatric concerns during the prenatal period, pregnancy offers an optimal time for early detection and intervention for perinatal mental health problems[44]. The American College of Obstetricians and Gynecologists recommends 13 care appointments during the prenatal period[45]. Evidence suggests that prenatal mental health interventions are effective at improving health outcomes and preventing psychiatric distress, but PPI is significantly under-identified and largely under-treated[46].

CURRENT RECOMMENDATIONS

In response to mounting concerns related to PPI and its impact on women and communities, initiatives to improve care have focused on universal screening. In the United States, the following organizations all recommend at least one screening for perinatal depression with a validated measure during the perinatal period: American College of Obstetricians and Gynecologists, American Academy of Pediatrics, United States Preventive Services Task Force (USPSTF), Centers for Medicare and Medicare Services, Council on Patient Safety in Women's Health Care[47-50]. The USPSTF specifies that screenings should only occur when there are significant resources for effective treatment and follow-up [51]. In the United Kingdom, universal screening is recommended by the National Institute for Health

and Care Excellence, though again, only when there are resources available for treatment and follow-up [52]. This is consistent with guidelines suggested by the World Health Organization in 2022[34] which suggested a stepped-care approach to the integration of perinatal mental health services into maternal health care. In Canada, universal screening is not recommended by the Canadian Task Force on Preventive Healthcare due to paucity of evidence for its benefits[53].

FOUR CHALLENGES ASSOCIATED WITH CURRENT RECOMMENDATIONS

Though there are some benefits to universal screening, including the low cost and low provider burden of having patients complete the forms, at least four major challenges have arisen with the current recommendations for universal screening in the perinatal period. Each challenge impacts all pregnant women, and each is also uniquely impactful in the outcomes of women of color.

Universal screening is not universally implemented

Unfortunately, screening has not been universally and systematically implemented in prenatal care, with estimates of screening by OB/GYN providers ranging from 39-72%[44,54,55]. Providers often do not assess for psychiatric illness for a number of reasons, including: (1) Lack of education regarding efficient measurement tools; (2) uncertainty regarding how to respond if a pregnant person endorses signs of perinatal psychiatric illness (PPI, and whether they will then be liable if negative outcomes occur); (3) lack of guidance regarding availability of appropriate treatment; (4) lack of time in short visits; and (5) lack of financial incentive for clinicians to screen[56,57].

There are notable racial disparities in the decision whether to screen for psychiatric distress. Women of color are 5%-10% less likely to be asked about psychiatric distress than White women[58,59], and without screening, women of color are less likely to spontaneously offer information regarding psychiatric distress due to discomfort and stigma[60].

Pregnant women underreport distress on psychiatric screenings

When screening does occur, many pregnant women underreport psychiatric distress. A qualitative review found that across several studies, many women reported that they did not have knowledge about PPI and were unaware that they would likely meet criteria given their current symptoms[61]. Other women who did recognize that they had symptoms of PPI reported being unable or unwilling to disclose feelings due to fear of burdensomeness, fear of giving their family a "bad name", and fear of losing their baby[61]. Many women had previously had symptoms dismissed or over-normalized (*i.e.*, described as normal aspects of the pregnancy period, a "rite of passage") and thus declined to disclose symptoms[62]. Other reasons to underreport symptoms include fear of disclosure outcomes, worry about being judged to be a bad mother, and lack of continuity of care[44,63]. Importantly, one study linked discomfort with being screened with higher scores on a depression scale, highlighting the relationship between experience of symptoms and discomfort with reporting them[64].

Limited data exist on differences in reporting of symptoms among pregnant women of different racial groups. However, women of color underreport psychiatric distress in non-pregnant samples, so it can be assumed they likely underreport symptoms during pregnancy[65].

Referrals are inconsistent

Women who do screen positive for psychiatric distress may or may not be given a referral to care, based on the clinic's access to resources and information. One program successfully engaged 80% of women who screened positive for depression symptoms in care, while another saw fewer referrals to care after universal screening was implemented than before[56,66].

Women of color who screen positive for psychiatric distress are not referred when appropriate as often as are White women. In one study, White women who disclosed psychiatric distress were referred for treatment twice as often as Asian and Black women[59]. In another, Hispanic/Latinx and Black women who met full criteria for depression were less likely to receive a depression diagnosis, limiting referrals[67]. Some studies show a 10% referral to treatment rate when women of color screen positive for psychiatric distress[68].

Follow-up after referrals is inconsistent

If they are given a referral to care, pregnant women do not follow up with treatment. In a study of referral rates, only approximately 40% of women referred attended even one visit[69]. Primary reasons for lack of follow-up include practical concerns (*e.g.*, perceived insufficient time, the inconvenience of attending appointments), perceived stigma (*e.g.*, feeling that needing help makes one a bad mother), and displeasure with how symptoms were handled by their provider (*e.g.*, feeling minimized, dismissed, or humiliated[61,62]). Pharmacological hesitancy is also noted in failure to follow-up, with many women worried about addiction, side effects, and stigma[62].

When resources might be available, women of color have significantly lower utilization rates of psychiatric services (*e.g.*, attendance at appointments, continued care and follow-up, medication management) than White women, even when controlling for age, type of psychiatric condition, and socioeconomic status[70-74]. Some researchers identify mental illness stigma as a potential contributor to these differences[75], as Black women perceive greater overall depression stigma than White women, regardless of personal experience with depression[76]. Furthermore, prior experiences with mental health treatment likely play a role in the attitudes of Black women seeking treatment during periods of psychological distress[77].

Though screening all women is the suggested standard of care in response to the mental health crisis in pregnant and postpartum women, these data demonstrate that universal screening is not sufficient for improving outcomes. Universal screening may even paradoxically serve as a barrier to care when delivered in its most common form (attached as a form to check-in paperwork). Without an explanation as to how the answers will be used, women (especially women of color) underreport symptoms to avoid negative outcomes[78].

In short and consistent with the Canadian Task Force on Preventive Healthcare, the current recommendations for universal screening are not effective for improving outcomes.

EQUITY-ORIENTED CARE

The above-described challenges inherent to universal screening reflect profound health inequities for pregnant women and especially pregnant women of color. Current standards of care (*e.g.*, universal screening and referral) were developed using the traditional medical framework, within which health inequities are increasing worldwide[79-81]. Even countries that provide universal health services to their citizens demonstrate major inequities based on race and ethnicity in their perinatal care. For example, in a large study in the United Kingdom examining over 600000 women who gave birth, Black African, Asian, and White non-British women had significantly lower access to outpatient mental health services than White British women[82]. Moving the needle on PPI and thus maternal mortality and morbidity will require approaches that are fundamentally aware of and responsive to health inequities in a way that traditional healthcare is not.

Equity-oriented care is positioned as an alternative to traditional care. It has been previously defined as "an approach that aims to reduce the effects of structural inequities, *etc.*; the impact of multiple and intersecting forms of racism, discrimination, and stigma (*e.g.*, related to mental illness, chronic illnesses, non-conforming gender and sexual identities, *etc.*) on people's access to services and their experiences of care; and the frequent mismatches between dominant approaches to care, *etc.*, and the needs of people who are most affected by health and social inequities"[83]. An equity-oriented framework is trauma-informed (recognizing the higher rates of trauma and violence in communities of color), culturally safe (explicitly addressing power dynamics and historical mistrust in the medical system), and contextually tailored (highlighting skills and education relevant to the medical system and community)[84].

Therefore, a successful perinatal mental health intervention would deviate from the traditional model of screening to refer and would follow an equity-oriented model. This model would specifically address mental health stigmatization and work to reduce systemic racism in the medical context while addressing practical barriers to accessing care. A direct way to meet both needs is to move away from universal screening and toward universal intervention.

UNIVERSAL INTERVENTION IN THE PRENATAL PERIOD

A universal intervention approach to psychiatric distress in pregnancy may eliminate known barriers to appropriate psychiatric management, thus improving trajectories for all pregnant women, and especially for women of color. Rather than losing women at every step of the screening-to-referral pipeline, provision of a universal intervention in the prenatal period ensures that evidence-based tools for prevention of PPI are delivered. Providing this intervention to all women is a novel approach to management of PPI.

Based on the accumulation of evidence regarding the most impactful interventions in the perinatal period, equity-oriented prenatal universal intervention should be trauma-informed[85] and limited to one 45-min session. This model is consistent with research suggesting that even one childbirth educational session is effective for improving outcomes and that requiring more sessions creates a barrier to psychiatric care[86,87]. It should be delivered in the prenatal period as either an adjunct to a standing prenatal appointment or as a separate appointment. It can be delivered by a mental health professional (*e.g.*, contracted, embedded, or other) or potentially by a trained OB/GYN provider (*e.g.*, nurse, MA, or other). Based on previous research regarding barriers to effective care as well as what is most helpful for women during the prenatal period, the universal intervention should include the following components: (1) Brief education about pregnancy and the childbirth process; (2) brief discussion of perinatal psychiatric issues in plain language; (3) discussion of trust and potential

discomfort with providers; (4) explanation of skills for maximizing healthcare appointments; and (5) list of free and low cost resources available throughout pregnancy and after childbirth. Components 1-4 could be created and disbursed as relevant for all pregnant women while component 5 needs to be individualized to the clinic based on location and institutional/community resources.

Brief education about pregnancy and the childbirth process

Various psychological techniques and theories suggest the importance of understanding stressors that lie ahead and managing them proactively (*i.e.*, stress inoculation training[88], dialectical behavior therapy[89]). Consistent with these theories, education should be provided regarding both the normal course of the pregnancy and childbirth process (including medically normal but potentially psychologically stressful situations such as transvaginal ultrasounds, manual cervical checks, and childbirth) as well as non-normal but still common situations (*e.g.*, gestational diabetes, preeclampsia, emergency c-sections). A respectful and informative overview of the pregnancy and childbirth phases will provide patients with an understanding of their course as well as allowing for prophylactic distress tolerance for the different situations.

Brief discussion of perinatal psychiatric issues in plain language

The average medical communication requires a level of health literacy (*i.e.*, ability to read and use medical information) that is higher than that of the average patient[90]. Improving mental health literacy, or knowledge about specific mental health conditions including early detection, has been suggested as a way to intervene earlier in the experience of psychiatric illness[91]. For this intervention, this would include providing patients with a plain language description of various PPI, including how they might experience them (in contrast to education for providers, which focuses more on how the provider might perceive symptoms).

Discussion of trust and potential discomfort with providers

Because limitations to screening include the likelihood of underreporting symptoms due to discomfort with and lack of trust in providers, an intervention should include a candid and humble discussion of this issue. Discussing common barriers to effective collaboration with providers (*e.g.*, experience of racism, fear of how shared knowledge will be used, previous traumatic medical experiences) may elucidate individual biases and difficulties that can be managed.

Explanation of skills for maximizing healthcare appointments

Patient empowerment is a crucial component of good medical care, and it is especially critical for vulnerable populations that tend to engage more passively in medical care[92]. Empowering women to utilize their medical appointments in the ways that they find most helpful can be done through providing simple skills and providing permission for their use. Skills should include bringing in questions written down ahead of time, recording appointments (with permission from provider), and asking for time for questions at the start of the appointment[93]. Skills also include emotion regulation skills to use when feeling anxious in the appointment.

List of free and low-cost resources available throughout pregnancy and after childbirth

A list of virtual and in-person options should be provided if the patient is interested in pursuing further behavioral health resources.

This method is equity-oriented in that it is trauma-informed, culturally safe (by explicitly addressing trust and discomfort with providers), and contextually tailored (discusses skills in plain language and ways to maximize healthcare appointments). It does not rely on women to overcome systemic barriers, fear and mistrust to risk disclosing painful experiences; rather, it offers information and education from a place of cultural humility and openness.

This method may confer a number of benefits over universal screening

Reduction of stigma: By delivering the intervention to all women, the information and education are considered standard components of prenatal care (similar to education about gestational diabetes) rather than specialized referrals based on problematic or unique disclosures. We expect that providers may see an increase in scores on screenings and in PPI diagnoses due to increased comfort with disclosing.

Increased preparation: The information provided within a universal psychological intervention should highlight events during the pregnancy and childbirth periods that may be uniquely stressful with an emphasis on identifying methods of coping in advance. This normalizes the potential reactions the pregnant person may have and allows them to prepare appropriately.

Increased mental health literacy: This intervention will provide general education about mental health concerns, which increases mental health literacy and reduces stigma.

Table 1 Advantages and disadvantages of universal screening and universal intervention

	Advantages	Disadvantages
Universal screening	Low cost; low provider burden	Patients likely to under-disclose; disparities in referrals and follow-ups; disparities in who receives resources and psychoeducation; reflects traditional model of healthcare; higher levels of care not always available if needed
Universal intervention	All patients receive psychoeducation and resources; mental healthcare is integrated into prenatal care; all patients have opportunity to discuss mental health concerns; will likely reduce costs long-term	Higher immediate cost; need for additional practitioners; higher levels of care not always available if needed

Increased comfort with help-seeking: By destigmatizing PPI and clearly explaining the importance of treating PPI, pregnant women may feel more comfortable seeking access to mental healthcare.

These interventions should be standard of care for all pregnant women.

CHALLENGES OF THIS MODEL

This model is not without its challenges. Systems-level barriers continue to exist, whether healthcare is privatized or nationalized. In low-, middle-, and high-income countries, challenges include low levels of funding afforded to mental health services, inequalities in levels of access to mental health care, and shortages of mental health providers[94,95]. Decisions will need to be made in clinic as to whether the intervention should be delivered by an embedded mental health professional (MHP) or by an OB/GYN provider. Benefits of delivery by an MHP are need for limited training, ability to provide ongoing care in clinic, and reduced burden on an already overburdened OB/GYN staff. Benefits of delivery by an OB/GYN provider are the low resources needed for implementation and reduction in the likelihood that the provider will divert responsibility for mental health management fully to the MHP, a frequent occurrence when MHPs are embedded in primary care[66]. Finally, this model does not address the major shortage of psychiatrists and mental health practitioners, both of whom are necessary when ongoing care is needed for more serious PPI management.

UNIVERSAL INTERVENTION *VS* UNIVERSAL SCREENING

As discussed above, universal intervention may address many of the concerns with universal screening. In summary, Table 1 discusses the advantages and disadvantages of universal screening (current state in many countries) and universal intervention (proposed model).

CONCLUSION

The application of a universal intervention model may de-stigmatize psychiatric care and address many of the barriers that continue to contribute to health disparities for women and especially women of color. Delivering a universal intervention to all patients, regardless of psychiatric distress within the context of prenatal care may improve individual and community outcomes for women by reducing stigma, increasing preparation, providing a connection to a psychiatric professional and improving mental health literacy. For women with psychiatric distress, a universal intervention may also provide a basic stress inoculation for pregnancy process, individualized referral to services if needed, and updated resources. If successful on a large scale, this intervention could contribute to changes in major international guidelines regarding the appropriate course of prenatal care.

FOOTNOTES

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Abstract

In recent years, epidemiological and genetic studies have shown an association between autoimmune diseases and psychosis. The question arises whether patients with schizophrenia are more likely to develop multiple sclerosis (MS) later in life. It is well known that the immune system plays an important role in the etiopathogenesis of both disorders. Immune disturbances may be similar or very different in terms of different types of immune responses, disturbed myelination, and/or immunogenetic predispositions. A psychotic symptom may be a consequence of the MS diagnosis itself or a separate entity. In this review article, we discussed the timing of onset of psychotic symptoms and MS and whether the use of corticosteroids as therapy for acute relapses in MS is unfairly neglected in patients with psychiatric comorbidities. In addition, we discussed that the anti-inflammatory potential of antipsychotics could be useful and should be considered, especially in the treatment of psychosis that coexists with MS. Autoimmune disorders could precipitate psychotic symptoms, and in this context, autoimmune psychosis must be considered as a persistent symptomatology that requires continuous and specific treatment.

Key Words: Multiple sclerosis; Psychosis; Schizophrenia; Corticosteroids; Antipsychotics

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Core Tip: Immunological perturbations in multiple sclerosis (MS) can lead to the development of psychotic symptoms. The use of corticosteroids and antipsychotics might prove beneficial and in patients with MS-related psychosis and outweigh their adverse effects.

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) that is characterized by neuroinflammation, demyelination, axonal loss and neurodegeneration[1]. It is one of the most common neurologic disorders and the most common cause of acquired neurological disability in young adults, that has an effect on 2.5 million people worldwide[2]. MS patients are two to three times more likely than the general population to suffer from mood and mental disorders[3,4].

Neurological and psychiatric diseases often overlap and co-occur[5,6]. Psychiatric symptoms may occur at any time during a neurological autoimmune disease, but they may also be an initial clinical manifestation and precede the onset of typical neurological symptoms[7]. The initial or early presence of these symptoms may complicate the establishment of a correct diagnosis, hinder the early recognition of the underlying brain disorder, and lead to inadequate treatment and a poorer prognosis[8,9]. Furthermore, the presence of various psychotic symptoms in neurological diseases additionally compromises these conditions and has an impact on individual functioning and overall disease burden [10]. The prevalence of psychosis/psychotic disorders is approximately 4.3%[11].

Mental disorders in neurological diseases may have different underlying causes[12]. In MS patients, the onset of psychiatric symptoms may be a consequence of the MS diagnosis itself[13]. Brain lesions, physical disabilities, symptoms of MS and pharmacological treatments may cause psychopathological manifestations[14].

There is limited scientific evidence that could be useful for clinical decision-making in the resolution of psychotic symptoms in patients with MS. Recent data by Sabe and Sentissi have confirmed our clinical observations[15]. There is a lack of data considering MS and psychosis, especially schizophrenia (SCH), simultaneously. We might think that this is due to a lack of interest in the field, but it is also possible that these disorders do not exist at their full capacity simultaneously. In this mini-review, we aim to resolve some clinical dilemmas. First, we discuss the timing of the onset of psychotic symptoms and MS. Second, whether the use of corticosteroids is unfairly neglected and whether a more aggressive treatment approach is warranted. And third, whether antipsychotics may be of benefit as adjunctive therapy is discussed. Immune disturbances may be similar or very different in terms of different types of immune responses, disturbed myelination, and/ or immunogenetic predispositions.

This mini-review was conducted through a systematic electronic search of the PubMed, Cochrane, and Web of Science databases to identify cases of MS with psychotic symptoms. The terms used were "multiple sclerosis"; "psychosis"; "schizophrenia"; "neurodegeneration"; "neuroinflammation"; "corticosteroids"; and "antipsychotics." We searched for studies published in English, with no restriction on year of publication. Experimental studies, randomized or nonrandomized clinical trials, cohort studies, and case-control studies were included. We have assessed the abstracts of potentially relevant titles and reviewed the full text of potentially eligible studies. In this mini-review, we attempted to select and focus on only up-to-date and clinically relevant data.

NEUROIMMUNOLOGICAL ASPECTS OF MS AND PSYCHOSIS

Genetic predisposition, individual and environmental factors, and specific immune responses had a significant impact on disease onset and clinical presentation. This suggests that the same etiological factors and pathophysiological pathways may influence the association between MS and psychosis. It raises the question of whether patients with SCH might also suffer from MS later in life. The genetic basis of MS is supported by the fact that the risk of disease is higher in MS family members than in the general population, that certain racial and ethnic groups have a lower illness tendency, and that the concordance rate is higher in monozygotic twins[16]. Previous genetic studies have shown that the predisposition to develop MS depends on several independent polymorphic genes and their interaction. No single gene variant is necessary or sufficient to cause MS, but each one increases the overall risk of the disease in an additive manner[17]. Genome-wide association studies (GWAS), which examine gene polymorphisms in the whole genome, suggest that over 200 gene loci that have different immune

functions are responsible for the development of MS[18,19]. The risk genes control the differentiation and state of these cells through their function in specific cellular processes in immune cells. In addition, recent evidence indicates that many immune cell populations are highly heritable, raising the possibility that MS risk genes define differences of immune cell populations that could also be involved in the pathogenesis of illness[18].

It is well known that the immune system plays an important role in the etiopathogenesis of MS and SCH[20,21]. Some authors assign them to the same group of neuroinflammatory and neurodegenerative properties, but with marked differences in the immune response. From the clinician's point of view, this fact could mean that these disorders are mutually exclusive. We have already considered confronting results of the prevalent immune responses in MS and SCH as prototypes of disorders of type 1 *vs* type 2 immune responses, respectively[22,23]. In recent years, growing epidemiological evidence has suggested a bidirectional association between autoimmune diseases and increased risks with SCH[24]. A family history of autoimmune disease has been shown to be related to an increased risk of psychotic disorders and vice versa[25]. In addition, having a first-degree relative with SCH increases the risk of autoimmune diseases by 6%[26]. Previous studies have found that patients with MS are at an increased risk of developing SCH[27]. SCH and other psychotic disorders have been associated with genetic markers of immune activation, suggesting a possible etiological link between MS and psychosis[28]. GWAS emphasized the significant overlapping of genes, noted the involvement of similar HLA alleles, and identified 21 independent loci associated with SCH and also associated with MS. In these diseases it seems that the major histocompatibility complex is responsible for the genetic overlap[29,30]. A possible additional role of genetics in this association could be an inherited susceptibility to common risk factors for infections or a predisposition to abnormal immune responses that further increases the risk of autoimmune reactions[31]. Despite the contrasting nature of these diseases, some common features have been identified. Risk factors for both MS and SCH include an interaction between genetic and environmental factors[32,33]. Infection is one of the most important triggers for the development of both diseases[34,35]. In the last decade, considerable attention has been paid to the gut microbiome as a possible etiological factor in the pathophysiology of MS and SCH[36]. It has been suggested that the composition of the intestinal flora plays an important role in CNS and immune system development [37]. Dysbiosis of the microbiome has been shown to affect the Th1/Th2 balance and the ratio of regulatory T cells to Th17 cells, which affects the immune response to pathogens[38,39]. Dysbiosis has been found to affect T cell-mediated inflammation in MS and SCH patients[40,41].

In SCH, it has been previously hypothesized that inflammation in the microvasculature persists as chronic, low-grade inflammation and does not disseminate in whole brain parenchyma as in acute encephalitis[21]. This organic substrate could be related to the soft neurological signs, observed in patients with SCH[42]. Similar to SCH, the clinical manifestations in MS may be the result of acute or chronic neuroinflammation. In the acute stage, the peripheral immune system is involved, and T cells, B cells, and macrophages enter into CNS and cause acute inflammation in the brain[21]. In addition, these mechanisms have no influence on the chronic phase. Recently, a concept of "compartmentalization" of the inflammatory process in the brain has been postulated, in which a local immune response in the CNS occurs separately from the peripheral immune system[43]. This hypothesis is supported by the fact that disseminated activation of microglial cells is the primary characteristic of the chronic phase of the illness[44]. There is ample evidence of biomarkers indicating a link between immunological processes, psychotic disorders and MS. Elevated levels of different inflammatory markers have been found in the blood and cerebrospinal fluid (CSF) of patients with psychosis and MS, with particularly high levels in patients with first-episode psychosis or acute relapse[45,46]. Dysregulation of regulatory T cells and Th17 cells may be essential for immunological homeostasis and play a role in the development of both diseases[47,48]. In recent years, much attention has been paid to B cells and their role in the autoimmune pathology of MS and psychosis[49,50]. Oligoclonal bands (OCBs) in CSF have been detected in approximately 90% of patients with MS[51]. In up 12.5% of patients with SCH were found OCBs[45]. It is important to keep in mind that there are other possible triggering and contributing factors besides the specifics of the immune response in MS and psychosis. Within the new concept of nomothetic network psychiatry and causal models, perhaps the identification of these transdiagnostic classes could even be presented as new nosological categories[52].

CLINICAL ASPECTS OF MS AND PSYCHOSIS

In clinical practice, it is important to distinguish whether psychosis precedes the onset of MS, coincides with MS, or is observed in the later stages of this somatic disease. We remind that these psychotic symptoms could be integral to SCH, a schizoaffective disorder, affective disorders, or even delirium. Also, we must point out that psychosis should be considered as a much broader concept than SCH. This information is important for the choice of future MS treatment.

Symptoms and signs of MS include ataxia, loss of coordination, hyperreflexia, spasticity, loss of visual acuity, sphincter incontinence, fatigue, anxiety, depression, and cognitive deficits[53]. Most patients have a relapsing-remitting form of the disease which is characterized by progression of symptoms in

relapse and possible further deterioration over time[53].

Neuropsychiatric symptoms were previously reported as a rare manifestation of MS. Recently, the most commonly observed behavioural disturbances preceding the onset of MS have been summarized. Symptoms described include lack of insight, delusions, auditory and visual hallucinations, mood disturbances, behaviour disorder, and confusion[15]. Psychotic symptoms reported in MS patients also include irritability/agitation, sleep disturbances, grandiosity, blunted affect, and rare symptoms such as catatonia and transient catalepsy[4,14].

In a recent systematic review of case reports and case series, the authors pointed out that psychotic symptoms preceded or accompanied the MS diagnosis in half of the cases, with a mean time to MS diagnosis of 0.8 ± 1.4 years, whereas 15.1% of MS diagnoses were discovered after isolated psychiatric symptoms. They observed a significant delay considering MS treatment initiation between initial psychotic symptoms and MS diagnosis (2.73 ± 3 years), and in patients with the first episode of psychos and MS diagnosis (0.8 ± 1.2 years)[15]. Another important observation in their analysis was that typical MS white matter lesions were found in a small group of patients with psychiatric disorders[54]. Finally, they pointed out that resistance or poor response to antipsychotics was associated with excellent improvement of both psychiatric and neurological symptoms with corticosteroids in most cases[15]. Autoimmune psychosis must be considered as a persistent symptomatology that requires continuous treatment[55].

Pathological changes in white and grey matter structures may play an important role in the pathogenesis of MS-related psychosis. Neuroimaging studies revealed that MS patients with psychotic symptoms have a higher total lesion score, especially in periventricular areas[56]. Psychotic symptoms in MS are correlated with a higher number or volume of lesions in the temporal or frontal lobes, cerebellum, and corpus callosum[57,58]. In addition, the presence of soft neurological signs in patients with sudden or acute psychotic symptoms without a prior personal or family history of psychosis is an indication for neurological exploration[15,59].

KNOWN FACTS AND TREATMENT CHALLENGES IN MS-RELATED PSYCHOSIS

Immunomodulatory medications for the treatment of MS could be useful to achieve remission of the disease, but in some cases may have a direct effect on the development of psychotic symptoms, although the mechanisms are poorly understood. This effect also occurs after initiation of corticosteroids or could be related with interferon beta (IFN-β) treatment. The study of 11 cases confirmed severe depression with suicidality in patients with MS, who were taking IFN-β and had no psychiatric history [60]. These patients also had phobic, aggressive, behavioural, psychotic, and manic symptoms, indicating the presence of a complex mood-behaviour disorder associated with IFN-β use. Complete remission of psychiatric complications was observed after discontinuation of IFN-β. Glatiramer acetate was generally not associated with deterioration of mood[61]. Gasim *et al*[62] conducted a systematic review to investigate whether the use of disease-modifying therapies is associated with adverse psychiatric effects in MS patients. This study included natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab and showed that their use do not increase risk of adverse psychiatric effects in MS, and some of them, such as fingolimod, even reduced the incidence of depressive symptoms. In addition, Krivinko *et al*[63] recently demonstrated that fingolimod treatment attenuated psychosis-associated behavioural deficits in rodents.

The standard MS treatment for acute exacerbations is pulse therapy with systemic glucocorticoids. Intravenous methylprednisolone at a dose of 1000 mg/d for 3 or 5 days or oral prednisone with or without tapering dose is usually used[64]. Administration of high-dose corticosteroids (HDC) may be repeated, depending on the MS course and disease activity[65]. Pulsed regimens of corticosteroid administration in the short term in MS have been reported to be well tolerated and safe, with only minor transient and dose- dependent side effects such as palpitations, hot flashes, dyspepsia, insomnia, and virulent taste[65].

An important clinical question is whether the use of corticosteroids, which are regularly used to treat MS relapses, can induce psychiatric symptoms. Several reports suggest that psychiatric side effects may occur with HDC use, including hypomania/mania, depression, psychosis, and suicidal ideation[66-71]. Mood changes, particularly (hypo)mania and depressive symptoms could be potentiated by HDC treatment[72]. In patients with MS, depression and mood disorders have been associated with pulse steroid therapy, suggesting that the risk may be related to the patient's psychiatric history[73].

Steroid-induced psychosis is a well-documented phenomenon[74]. In clinical practice, there are different approaches to corticosteroid treatment for MS-related psychosis. The literature on the treatment of corticosteroid-induced psychosis is very scarce and limited to MS reports and small-sample size studies. In our country, the prevailing opinion is that patients with psychosis should not be treated with corticosteroids because they may exacerbate psychosis. Moreover, nearly 30% of patients in the acute phase of their psychotic symptoms were successfully treated with corticosteroid therapies[75]. The question arises whether it is more beneficial for the patient to keep the psychosis under control or to treat the acute relapse, act on the inflammation, and prevent further disease progression and

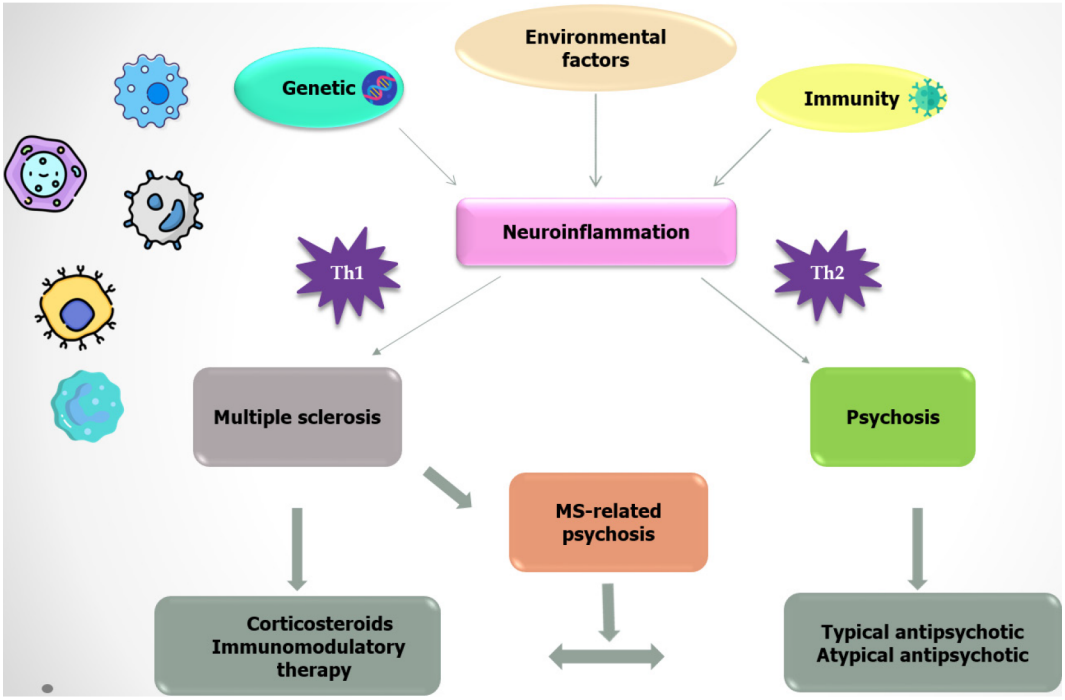
neurological disability. The Maudsley guideline indicates that the benefits of corticosteroid therapy may outweigh its adverse effects[76]. To date, however, few studies have explored the impact of corticosteroid therapy on psychosis in people affected by MS, and the specific risk factors predictive of psychiatric changes remain unclear[72,77]. Chronic consumption of corticosteroids and increase in their dose and duration of treatment are associated with these adverse effects[78]. As frequently mentioned, a general therapeutic strategy for corticosteroid-induced psychiatric symptoms should begin with dose reduction or discontinuation of the drug whenever possible[69,79].

Corticosteroid-induced hypomania, mania, and mixed mania showed to be successfully treated with a typical antipsychotic or mood stabilizer, most commonly haloperidol, haloperidol plus lithium, quetiapine, risperidone, olanzapine, olanzapine with valproate, carbamazepine, lithium, lamotrigine plus clonazepam, or clonazepam alone when lithium was ineffective[68]. In some cases, a combination of an antipsychotic and a benzodiazepine was needed[68]. In the case of medication-induced psychosis, adjustment of the MS drug should be considered and treatment with an antipsychotic should be initiated. There are few practical guidelines for the choice of antipsychotic drug and dosage, but there is evidence of good results with the use of clozapine, risperidone, ziprasidone, low-dose chlorpromazine, or the prophylactic use of lithium along with corticosteroid therapy[80]. In patients with steroid-induced psychosis, use of the antipsychotic quetiapine resulted in decreased irritability, reduced psychological distress, and improved sleep[81]. Atypical antipsychotics remain the treatment of choice in these patients because they have a more favourable tolerability profile, as they are less likely to affect the extrapyramidal system and reduce the risk of developing pseudoparkinsonism and catalepsy[82, 83]. Researchers also presumed that patients with MS had an unexpected sensitivity to antipsychotic drugs[84]. MS is closely related to various movement disorders[85]. However, clinicians should be aware that movement disorders can also represent adverse drug reactions caused by chronic antipsychotic therapy[86], especially in cases of polypharmacy.

The anti-inflammatory potential of antipsychotics could be useful and should be considered especially in the treatment of psychosis that coexists with MS. Patients with SCH have been found to have decreased intracortical myelination, whereas certain antipsychotic agents may restore this defect. Patergnani *et al*[87] showed that human and experimental MS induce a mitochondrial deficit leading to activation of autophagy and mycophagy. These phenomena play a causal role in MS as their inhibition by antipsychotic drugs such as haloperidol and clozapine may prevent demyelination, induce remyelination, and reverse MS behavioural deficits[87]. In addition, Stamoula *et al*[88] argued that the atypical antipsychotics clozapine, risperidone, quetiapine, and olanzapine dramatically reduce the severity of experimental autoimmune encephalomyelitis and delay its onset by downregulating the production of pro-inflammatory cytokines and chemokines and attenuating T-cell infiltration, myeloid cell activation, and upregulation of T regulatory cells.

CONCLUSION

Psychotic symptoms could represent an acutisation of MS, considering the specific localization of the lesions. In this context, it can be assumed that causal therapy of MS also leads to resolution of psychosis. It is also important to exclude somatic comorbidities to make the diagnosis of SCH. Autoimmune disorders could precipitate psychotic symptoms, and in this context, special attention should be paid to patients with the first psychotic episode and soft neurological signs, sudden cognitive decline, and unsatisfactory response to antipsychotic treatment. Only when all of the previously mentioned facts have been ruled out can one conclude that psychosis is a separate entity (Figure 1). Physicians treating patients with MS and psychosis should assume, first and foremost, that the psychotic syndromes are related to MS and not triggered by medication. Based on the literature data, it is extremely important for clinicians to perform accurate screening of psychiatric status in patients with MS before initiating HDC treatment and to note that HDC should be used with caution in patients with an acute MS exacerbation. The properties and indications of available immunomodulatory drugs need to be better understood, and the therapeutic approach should be adjusted with careful consideration of the individual's unique constellation of symptoms. The mechanism of action and pharmacokinetics of the antipsychotic drug, the safety and efficacy profile from clinical trials, and knowledge of potential side effects should also be incorporated into the therapeutic strategy.



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Figure 1 Etiopathogenesis of multiple sclerosis, psychosis, and multiple sclerosis-related psychoses and potential treatment options. Environmental factors, genetics, and immune disturbances lead to different types of immune responses that cause neuroinflammation, which is an underlying mechanism in the development of multiple sclerosis (MS) and psychosis. Inflammatory changes that occur in MS may induce psychotic symptoms. Corticosteroids and antipsychotics may be beneficial in patients suffering from MS-related psychoses. Th: T helper; MS: Multiple sclerosis.

FOOTNOTES

Author contributions: Vesic K has presented the idea; Vesic K and Borovcanin M structured the manuscript; All authors searched the literature in their scope of interest and competencies; Vesic K incorporated all parts of the manuscript and drew a figure; The authors gave final suggestions and approval for the final version of the manuscript.

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ORIGINAL ARTICLE

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Relationship between perceived social support and post-traumatic growth in coronavirus disease 2019 patients discharged from the hospital

Meltem Şirin Gök, Bahar Çiftçi

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has affected mental health and physical health negatively in some individuals. Examining perceived social support and post-traumatic growth (PTG) in COVID-19 patients could facilitate our understanding of how patients maintain their mental health.

AIM

To examine the relationship between the level of perceived social support and PTG in COVID-19 patients discharged from the hospital.

METHODS

This descriptive study was carried out between August and September 2022 with patients who were hospitalized due to COVID-19 in a university hospital in Erzurum and who were discharged at least 3 mo prior to the beginning of the study. The study was completed by 196 patients. Study data were collected face-to-face using a personal information form, multidimensional scale of perceived social support and PTG inventory.

RESULTS

The total mean score of the multidimensional scale of perceived social support was 63.82 ± 15.72. The PTG inventory total mean score was 47.77 ± 19.85. In addition, a direct significant correlation was found between perceived social support in COVID-19 patients and PTG.

CONCLUSION

The study results showed that perceived social support variables affected PTG

significantly. Therefore, it is recommended for healthcare professionals to implement interventions to promote social support from healthcare professionals and the patient's family and friends. Considering the negative effects of the ongoing COVID-19 pandemic, it is very important and necessary to implement effective public health interventions to promote PTG to reduce mental health problems.

Key Words: COVID-19 patients; Perceived social support; Post-traumatic growth; COVID-19

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Core tip: Since post-traumatic growth (PTG) includes development at the level of psychosocial functionality, it can contribute to personal development by positively affecting psychological and social factors after traumatic events. Social support positively affects an individual's mental health and PTG. The results of this study remarkably showed that there is a significant relationship between perceived social support and PTG. More studies are needed to confirm this observation.

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INTRODUCTION

The symptoms are variable in individuals diagnosed with coronavirus disease 2019 (COVID-19). Some individuals were asymptomatic, while the disease may progress from mild pneumonia to severe and fatal acute respiratory failure[1]. This disease affects the physical, psychological and social well-being of individuals[2]. Fear of death, hospitalization in the intensive care unit, endotracheal intubation, pain, limited communication, environmental stress, insomnia, impaired comfort, quarantine measures, feeling of loneliness, loss of control and stigmatization are among the different stressors of the COVID-19 pandemic[3]. A diagnosis of COVID-19 and hospitalization are considered the greatest of these stressors and accepted as a traumatic life experience[4]. While traumatic events cause serious mental problems such as anxiety, depression and post-traumatic stress disorder in some individuals[5], they may result in post-traumatic growth (PTG) in some[6]. PTG is defined as positive psychological changes as a result of a major life crisis or struggle with a traumatic event[7]. These changes occur in areas of improved interpersonal relationships, new opportunities, a greater sense of personal power, a greater appreciation of life and spiritual change[7].

The rapid increase in the number of COVID-19 cases and deaths has been reported to cause stress, fear, anxiety and depression in many people[8]. However, as individuals try to understand negative experiences and adapt to difficulties, positive reactions may also occur[9]. After the diagnosis of a severe disease, most survivors experience various positive changes that reflect useful psychological adaptation and positive personal development processes that enable them to better cope with the disease[7]. In a qualitative study, it was found that patients with severe COVID-19 showed negative emotional reactions in the early periods of the disease, while the disease resulted in psychological growth over time. The patients met the problems gratefully by cherishing their lives and their families[3]. Since PTG includes development at a psychosocial functionality level, it may contribute to personal development by positively affecting psychological and social factors after traumatic events[10]. In this context, social support is a source of resilience that positively affects individual mental health and facilitates PTG[11-13].

Measures taken during the COVID-19 pandemic, such as quarantine and social distancing, have led to differentiation in many areas of life. For this reason, individuals could not socialize at desired levels, and they faced problems such as social isolation and loneliness[14]. Similarly, in one study, social support was determined to be a psychological factor that made patients stronger[3]. Social support often refers to the care or support individuals receive from others or the feeling of belonging to a social network that provides mutual help[13]. To date social support has been broadly construed in two ways: perceived social support and received social support[15]. Perceived social support concerns the subjective evaluation of how individuals perceive friends and family members as available to provide material, psychological and overall support during times of need, whereas received support relates to the actual quantity of support received. This distinction between these two types of support is important for two reasons[15].

Social support in the face of stress can act in two different ways. In the buffer effect model, it is reported that social support reduces or balances the damaging effects of stress on physical and mental health as a buffer, especially in protecting physical and psychological health of people who are exposed to stressful experiences. In the basic impact model, social support has an effect independent of the level of stress, and there is a direct relationship between social support and health[16]. According to this approach, social support can increase life satisfaction and prevent or reduce stressful life events by providing a sense of belonging. Thus, with this effect of social support, the person experiences fewer physical and psychological problems[17]. Looking at the models that explain the relationship between psychological problems and social support, it is emphasized in the social causality model that lack of social support causes psychological symptoms. According to the social choice model, the individual's psychological symptoms cause the sources of social support to change. Finally, in the mutual effect model, while social support is effective on psychological well-being, the psychological state of the individual is also effective on accessing adequate social support. In other words, there is a bidirectional relationship between social support and psychological symptoms[18].

During COVID-19 treatment, the importance of psychosocial intervention is emphasized in both recovery and reducing psychological problems[13]. Studies conducted have reported that social support has an effect on improving psychological problems[12]. Psychological effects of contagious diseases may continue or develop over time. It has been found that individuals with high social support perception have fewer negative psychological consequences[11]. Social support is thought to be important for mental health in the post-discharge follow-up of COVID-19 survivors. Nurses, who are continuous interacting with patients, have important responsibilities in identifying traumatized individuals, increasing the support they need and empowering them in this process. Since the COVID-19 pandemic has negatively affected mental health and physical health, examining PTG and social support in COVID-19 patients will facilitate our understanding of how patients protect their mental health[19].

On the other hand, it is widely believed that high perceived social support predicts high PTG[15,20,21]. Given that several studies have reported that people often feel isolated and alienated and have difficulty accessing social support when diagnosed with COVID-19[22], there is a need to further clarify the role of perceived social support within PTG during COVID-19. In light of all this information, the aim of this study was to examine the relationship between the level of perceived social support and PTG in COVID-19 patients discharged from the hospital.

Research questions

What are the perceived social support levels of COVID-19 patients discharged from the hospital?

What are the PTG levels of COVID-19 patients discharged from the hospital?

Is there a relationship between perceived social support and PTG in COVID-19 patients discharged from the hospital?

MATERIALS AND METHODS

Study design

This study was conducted with a descriptive and a cross-sectional design.

Place and time of the study

The study was conducted at Atatürk University Research Hospital between August 2022 and September 2022.

Population and sample of the study

The population of the study consisted of patients who were discharged after receiving COVID-19 treatment at Atatürk University Research Hospital. Before starting the study, a sufficient number of sample was calculated for correlation analysis with the G Power 3.1.9.7. Package program. Since no similar study was found in the literature, priori power analysis was performed based on a moderate effect size (0.3). In the power analysis based on alpha of 0.05 and power of 0.99, it was determined that the sample size should be 195. For this reason, the study was completed with 196 patients.

Inclusion criteria

(1) Patients who were treated in the hospital with a diagnosis of COVID-19 and who had been discharged at least 3 mo prior to study enrollment; (2) Patients older than 18 years of age; and (3) Patients who did not have cognitive disabilities.

Data collection tools

Study data were collected by using a personal information form, multidimensional scale of perceived social support and PTG inventory.

Personal information form: This form was prepared by the researchers to find out the demographic characteristics of discharged COVID-19 patients and COVID-19-related characteristics. This form consisted of questions such as age, sex, educational status, marital status, number of children and level of income.

Multidimensional scale of perceived social support: The scale was developed by Zimet *et al*[23]. A Turkish validity and reliability study of the scale was conducted by Eker *et al*[24]. The scale is a 7-point Likert type self-report consisting of 12 items and 3 subscales. The subscales are family support, friend support and significant other support. Each item is evaluated between 1 and 7. The minimum possible score from the scale is 12, while the maximum possible score is 84. A higher score means higher perceived social support. Internal consistency of the scale is between 0.80 and 0.95 for the total scale and the subscales[24]. Cronbach's alpha value was 0.93 for the present study.

PTG inventory: The inventory was developed by Tedeschi *et al*[5]. The scale consists of a total of 21 items and 5 factors. The scale factors are improved relationships, new possibilities, personal strength, spiritual growth and appreciation for life. Internal consistency coefficient of the original scale is 0.90, while internal consistency coefficients of the factors vary between 0.67 and 0.85[5]. PTG inventory was adapted into Turkish by Dürü *et al*[25]. The scale is a 6-point Likert type scale. Scoring system is between 0 (I did not experience this change) and 5 (I experienced this change to a very great degree). It was stated in the Turkish adaptation that the 5-factor structure was preserved, and this structure explained 67.84% of the total variance. Score range of the scale is between 0 and 105. Higher scores from the scale mean higher PTG. Cronbach's alpha was 0.93 in the Turkish adaptation study[25]. Cronbach's alpha was 0.94 in the present study.

Data collection

Study data were collected with the face-to-face interview technique. After the purpose of the study was explained, the questions in the data collection tools were asked one by one, and the answers of the patients were recorded. Data collection lasted approximately 15 min for 1 patient. Consent was given by the patient prior to data collection.

Data assessment

Data analysis was performed using SPSS version 22.0. Frequency, percentage, mean and standard deviation measurement were used for descriptive statistics. Normality distribution of the data was analyzed with skewness and kurtosis coefficients. Pearson's correlation analysis was used for the examination of the comparison between the two scales. Cronbach's alpha was evaluated to test the reliability of the scales. A P value of 0.05 was considered statistically significant. Post-traumatic effect of perceived social support was analyzed with a simple linear regression analysis.

Ethical considerations

Ethical approval was obtained from the Ethics Committee of Atatürk University Faculty of Medicine to conduct the study. Written institutional permission was also obtained from Atatürk University Research Hospital for data collection. Oral and written informed consent was obtained from the patients.

Limitations of the study

The first limitation of the study was the collection of data with self-report scales. Another limitation was that PTG symptoms were not evaluated by a mental health professional but by the self-reports of the patient. Since the results depended on data collected from COVID-19 patients discharged in the Eastern Anatolia region of Turkey, it is not suitable for the results to be generalized to COVID-19 patients from other regions.

RESULTS

Mean age of the patients was 50.05 ± 19.19. It was found that 57.1% of the patients were male, 73.0% were married, 75.0% had children, 66.8% had nuclear family, 60.7% lived in a city center, and 59.2% were primary education graduates. It was found that 45.9% of the patients were unemployed and 57.7% had income equal to expenditure. It was found that 70.4% of the patients were treated in the COVID-19 clinic, treatment lasted for an average of 13.22 ± 10.46 d, 52.6% received oxygen therapy, and an average of 12.67 ± 5.93 mo passed after being discharged. We observed that 63.3% of the patients did not have a chronic disease, and 78.1% were not hospitalized for any other reason after discharge from COVID-19. In addition, it was found that 55.6% of the patients lost a close friend due to COVID-19, 93.3% did not receive psychological help from any expert due to COVID-19, and 87.2% had been vaccinated for COVID-19 (Table 1).

Table 1 Sociodemographic characteristics of the patients, *n* (%)

Characteristics	
Sex	
Female	112 (57.1)
Male	84 (42.9)
Marital status	
Single	53 (73.0)
Married	143 (27.0)
Children	
Yes	147 (75.0)
No	49 (25.0)
Family type	
Nuclear family	131 (66.8)
Extended family	65 (33.2)
Living place	
Village	45 (23.0)
District	32 (16.3)
Province	119 (60.7)
Education status	
Primary education	116 (59.2)
High school	39 (19.9)
University or graduate	41 (20.9)
Income status	
Less than income	40 (20.4)
Income is equivalent to expenses	113 (57.7)
More than income	43 (21.9)
Working status	
Yes[1]	90 (45.9)
No[2]	106 (54.1)
Chronic disease	
Yes	72 (36.7)
No	125 (63.3)
Treatment place	
Intensive care unit	46 (23.5)
Clinic	138 (70.4)
Both	12 (6.1)
Form of treatment	
No support	89 (45.4)
Oxygen therapy	103 (52.6)
Noninvasive-invasive ventilation	4 (2.0)
Lost a loved one due to COVID-19	
Family	31 (15.8)
Relative	56 (28.6)

Close friend	109 (55.6)
Hospitalization for another reason	
Yes	43 (21.9)
No	153 (78.1)
Received psychological support from a specialist due to COVID-19	
Yes	12 (6.1)
No	184 (93.9)
Availability of COVID-19 vaccine	
Yes	171 (87.2)
No	25 (12.8)
Age, mean ± SD	50.05 ± 19.19
Treatment duration (d), mean ± SD	13.22 ± 10.46
Time elapsed after COVID-19 treatment (mo), mean ± SD	12.67 ± 5.93
Stress level related to COVID-19, mean ± SD	7.14 ± 2.58

[1]Officer, self-employed, student.
[2]Housewife and those who do not work in another job.
COVID-19: Coronavirus disease 2019.

The total mean score of the multidimensional scale of perceived social support was 63.82 ± 15.72. The mean subscale scores of the multidimensional scale of perceived social support were 20.22 ± 6.27 for family support, 20.85 ± 5.80 for friend support and 22.74 ± 4.71 for significant other support.

PTG growth inventory total mean score was 47.77 ± 19.85. When the factors were examined, the mean scores were 13.87 ± 5.57 for improved relationships, 8.52 ± 3.82 for new possibilities, 8.81 ± 4.71 for personal strength, 9.20 ± 4.35 for spiritual growth and 7.34 ± 3.43 for appreciation for life (Table 2).

A weak, yet significant, positive correlation was found between family support and improved relationships, new possibilities, personal strength and total PTG scale ($P < 0.05$). In the significant other subscale of perceived social support, no significant correlation was found between total PTG scale and subfactors ($P > 0.05$). A weak, yet significant, positive correlation was found between perceived social support total score of the patients and improved relationships, new possibilities, personal strength and total PTG scale ($P < 0.05$) (Table 3). According to the results of the simple linear regression analysis, it was found that perceived social support significantly and positively predicted the PTG levels of the discharged COVID-19 patients (β = 0.159, $P < 0.05$). According to the model, perceived social support explained 2.5% of the total variance in PTG ($R^2 = 0.025$ F = 5.026, $P < 0.05$) (Table 4).

DISCUSSION

In this study, which examined the relationship between the perceived social support level of COVID-19 patients discharged from the hospital and PTG, it can be seen that the patients had a good level (63.82 ± 15.72) of perceived social support (between 12 and 84) (Table 2). Social support was defined as the support available to the individual through social relationships with others. Social support from health professionals and health institutions is an effective factor in this regard[26]. A study by Moodi *et al*[27] showed that patients' perceived social support scores were high. Zhang *et al*[28] found increased support from friends and family during the COVID-19 outbreak. Thompson *et al*[29] found that social support increased in discharged COVID-19 patients. In the study of Kandeğer *et al*[30], COVID-19 patients were found to have high perceived social support. Alnazly *et al*[31] concluded that patients had high social support levels.

Health personnel became an important source of support for patients due to lack of direct communication between the patient and family members during their hospitalization. In addition to the support of family members, patients also receive support, such as education and counselling, from the health system. All these services may have played an important role in the formation of perceived social support. Increased perceived social support may subsequently positively influence PTG. Positive developments during the pandemic, such as the development and dissemination of the vaccine, may have helped to eliminate the negative emotions of COVID-19 patients and to create positive coping styles of the patients.

Table 2 Multidimensional scale of perceived social support and post-traumatic growth scale sub-scale and mean, minimum and maximum values of total score averages

Scales	Minimum and maximum scores that can be obtained from the scale	Minimum and maximum scores taken from the scale	mean ± SD
MSPSS			
Family support	4-28	4-28	20.22 ± 6.27
Friend support	4-28	7-28	20.85 ± 5.80
Significant other support	4-28	4-28	22.74 ± 4.71
Total MSPSS	12-84	24-84	63.82 ± 15.72
PTGS			
Relationships with others	0-30	0-30	13.87 ± 5.57
New possibilities	0-20	0-18	8.52 ± 3.82
Personal strength	0-20	0-20	8.81 ± 4.71
Spiritual change	0-20	0-20	9.20 ± 4.35
Appreciate life	0-15	0-15	7.34 ± 3.43
Total PTGS	0-105	0-100	47.77 ± 19.85

MSPSS: Multidimensional scale of perceived social support; PTGS: Post-traumatic growth scale.

Table 3 Relationship between post-traumatic growth scale and multidimensional scale of perceived social support

Relationship	Family support		Friend support		Significant other support		Total MSPSS	
	R	*P* value	R	*P* value	R	*P* value	R	*P* value
Relationships with others	0.177	0.177	0.151	0.035[a]	0.132	0.064	0.166	0.020[a]
New possibilities	0.163	0.023[a]	0.155	0.030[a]	0.125	0.08	0.16	0.025[a]
Personal strength	0.142	0.048[a]	0.135	0.059	0.126	0.078	0.144	0.044[a]
Spiritual change	0.135	0.06	0.085	0.239	0.069	0.335	0.106	0.141
Appreciating life	0.127	0.077	0.141	0.048[a]	0.123	0.085	0.14	0.051
Total PTGS	0.166	0.020[a]	0.147	0.039[a]	0.128	0.074	0.159	0.026[a]

[a]Correlation was significant at the 0.05 level (two-tailed).
R: Pearson's correlation; MSPSS: Multidimensional scale of perceived social support; PTGS: Post-traumatic growth scale.

Table 4 Perceived social support as predictors of post-traumatic growth

Parameter	B	Standard error	β	*t*	*P* value	R^2	Adjusted R^2
Total PTGS	34.969	5.880		5.947	0.000		
Total MSPSS	0.201	0.089	0.159	2.242	0.026	0.025	0.020

R = 0.159, R^2 = 0.025, F = 5.026, $P < 0.05$, Durbin Watson: 2.100. MSPSS: Multidimensional scale of perceived social support; PTGS: Post-traumatic growth scale.

In this study, it was found that the individuals had moderate (47.77 ± 19.85) PTG (between 0 and 105) (Table 2). Although there are few studies on PTG in COVID-19 patients who have survived after admission to the intensive care unit, these results are in line with previous studies. Therefore, the present study showed that PTG may be important in patients treated in an intensive care unit for COVID-19. In another study, it was found that patients hospitalized in the intensive care unit with a

COVID-19 diagnosis experienced PTG close to a moderate level after treatment[32]. In a study conducted on discharged COVID-19 patients, Thompson *et al*[29] showed moderate PTG. The most important step for post-traumatic development is that individuals do not see themselves as trauma victims but as post-traumatic survivors. Tedeschi *et al*[5] suggested that initial stress is induced by traumatic events, which encourages individuals to challenge and rebuild (existing) schemas and assumptions, which then results in positive changes. However, one of the important points is that the evaluation of PTG symptoms by the patient's own reports, not by a mental health professional, may have affected this result. For this reason, the importance of the findings of this study will be emphasized, and the evaluation of the patient by both their own PTG and mental health experts will strengthen the results.

According to Tedeschi *et al*[5], social support plays an important role in the transition from trauma to growth since it activates the cognitive processes that support PTG. It can be especially valuable for COVID-19 patients to have the opportunity to express themselves in a supportive environment and to get help in any adversity they experience. Social support is associated with better physical and psychological health. The correlation between patients' perceived social support and PTG and the factors of improved relationships, new possibilities and personal strength was found to be positive but weak (Table 3). In the study by Gökahmetoğlu *et al*[33], no correlation was found between perceived social support and PTG. In a study conducted by Hill *et al*[34] on cancer patients, it was concluded that social support was not a predictive variable in PTG. In a study conducted on patients with different traumatic experiences, Dürü *et al*[25] found that social support did not have an effect on PTG.

On the other hand, perceived social support and PTG were found to be positively correlated in our study. In the study by Sun *et al*[3], it was stated that during quarantine periods individuals benefited from the emotional support they received from their families as well as the support provided by their colleagues and neighbors. Similarly, in a study conducted with individuals diagnosed with COVID-19 and discharged in China, it was determined that social support systems were positively related to PTG [29]. In a study examining the quarantine experiences of COVID-19 patients, it was stated that the social support patients received from their families and friends made a significant contribution to coping with negative emotions[35]. In a study by Lohiniva *et al*[36], some patients mentioned some positive developments such as feeling closer to their spouses and spending more time as a family during the quarantine period. A high level of perceived social support affects the individual's ability to provide a sense of having a safe environment, to emphasize their sense of belonging, to act as a buffer against stress, to provide new meanings and to create more positive perceptions that support growth. While perceived social support facilitates adaptation to cognitive processes, it also supports individuals to effectively manage coping strategies in identifying positive situations for their personal development.

Being diagnosed with COVID-19, physical symptoms caused by the disease and quarantine practices can cause many changes in individuals, especially spiritually. It is thought that the uncertainty about the disease and the treatment process, the fact that the disease can be fatal and the restrictions on daily life cause personal changes in individuals. Especially in this process, it has been observed that individuals experience many personal changes such as changes in life philosophy and perspective, changes in life priorities, strengthening in self-perception and appreciating and being grateful for what they have. It is thought that the differences between study results are due to the scales used, inclusion criteria and the way individuals perceive and evaluate social support. This positive change experienced by individuals may have led them to emerge stronger from the crisis created by the pandemic. Findings showed that increasing perceived social support can contribute to PTG.

Another remarkable finding is that the most significant growth in PTG was in the spiritual subdimension (Table 2). A sample of parents in Portugal during the pandemic found high rates of PTG, particularly in the areas of appreciation for life and improved relationships[37]. In the study by Liu *et al* [38], some patients stated that COVID-19 supported their personal development and motivation for a better life in the future. It is thought that this difference is due to Turkish culture, religious differences and customs. In this context, COVID-19 diagnosis may cause an individual change and empowerment in patients. In the present study, it was suggested that patients' life priorities and philosophies have changed and that they will prioritize their health.

CONCLUSION

In the present study, which examined the relationship between perceived social support level of COVID-19 patients discharged from the hospital and PTG, it was found that patients had a good level of perceived social support and a moderate level of PTG. A significant correlation was also shown between perceived social support of the patients and PTG. Since there are few studies examining the relationship between these variables in the literature, it is important to conduct more studies to confirm these findings. It may be useful to repeat the research with larger samples. Prospective and longitudinal studies are recommended to further confirm the versatility of the findings and to elucidate the factors influencing PTG. Since these findings include subjective evaluations of patients, it is recommended to plan new studies in which the results are also evaluated objectively by mental health professionals.

Relevance for clinical practice

It is known that a large number of people have been affected by the COVID-19 pandemic, especially patients in the intensive care unit. The high impact of the traumatic event, although at least 3 mo have passed after being discharged from the intensive care unit due to COVID-19, may be associated with the continuation of the pandemic process and the increase in the number of patients. Therefore, considering the adverse mental health impacts of the ongoing COVID-19 pandemic, it is crucial to implement effective public health interventions to promote PTG and reduce mental health issues.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic has affected the mental health of individuals. There is a controversial relationship between perceived social support and post-traumatic growth (PTG).

Research motivation

There are few studies that show the relationship between perceived social support and PTG in COVID-19 patients.

Research objectives

To examine the relationship between the level of social support perceived and PTG.

Research methods

This descriptive study was carried out between August and September 2022 with patients who were hospitalized due to COVID-19 and who were discharged at least 3 mo prior to the beginning of the study. The study was completed by 196 patients. Study data were collected face-to-face using a personal information form, multidimensional scale of perceived social support and PTG inventory.

Research results

It was found that patients had a good level of perceived social support and a moderate level of PTG.

Research conclusions

Perceived social support positively affects PTG.

Research perspectives

Further research is needed to confirm these results. In the future, mental health specialists should evaluate individuals for PTG.

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FOOTNOTES

Author contributions: Şirin Gök M contributed to the data analysis; Şirin Gök M and Çiftçi B contributed to the study design, data collection, study supervision, manuscript writing and critical revisions for important intellectual content.

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SYSTEMATIC REVIEWS

Use of new technologies for the promotion of physical activity in patients with mental illness: A systematic review

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Abstract

BACKGROUND

Physical exercise is an underutilized tool for the management of mental disorders. New technologies have made a breakthrough in health care, and one of its possible applications (apps) could be that of customizing exercise programs for special populations, such as patients with mental disorders. However, the app of the so-called e-health to mental health care is still limited.

AIM

To know the efficacy of apps to promote physical activity in patients with mental disorders.

METHODS

We conducted a systematic review of the PubMed and Embase databases with the aim of exploring the use of new technologies for the enhancement of physical exercise in patients with a psychiatric illness. Following the selection process, 10 articles were included in the review.

RESULTS

The most commonly used devices in this type of intervention are wearable devices and web platforms. Good results in terms of effectiveness and acceptability were obtained in most of the studies.

CONCLUSION

Our findings suggest that the use of new technologies in mental health represents a feasible strategy with great potential in clinical practice.

Key Words: e-health; m-health; Physical exercise; Mobile applications; Wearable device

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Core Tip: Physical exercise is an underutilized tool for the management of mental disorders. New technologies have made a breakthrough in health care, and one of its possible applications (apps) could be that of customizing exercise programs for special populations, such as patients with mental disorders. Apps that aim to improve and increase physical activity in patients diagnosed with the disease have shown good results in terms of efficacy and acceptability, so they should be known by clinicians in order to offer them to patients who meet a good profile.

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INTRODUCTION

Mental illness is one of the major global public health problems[1]. People with severe mental disorders are in poorer health, with more cardiovascular risk factors and high morbidity and mortality rates. Factors associated with this poorer health status include a greater tendency to lead a sedentary lifestyle and high comorbidity with chronic physical illnesses[2-4]. Furthermore, mental disorders often do not access the health care they require and, even when they do, treatment is often inadequate[5].

The relationship between physical health and mental illness can also be harnessed to our advantage and contribute to closing the gap in the treatment of these disorders: Numerous studies show the benefits of physical exercise on mental state[6-14]. In a recent population-based survey in Spain, physical exercise was inversely associated with major depressive disorder (MDD), irrespective of body mass index[6]. Several studies have investigated the therapeutic potential of physical exercise in other mental disorders such as anxiety, post-traumatic stress disorder, or even psychotic disorders[7-12]. Finally, several randomised clinical trials agree on the antidepressant effect of physical exercise[13,14].

However, it is difficult to inculcate physical exercise habits in people with psychiatric symptoms, especially in the acute phases of the illness. New technologies can make this task easier. Digital medicine, also called e-health, is opening new horizons in the management of a multitude of diseases, including MDD[15]. The enhancement of physical activity is one of the most exploited functions by this type of technology that is based on applications (apps) and software programmes managed through various platforms, such as websites, wearable devices, smartphones, or social networks. Some of these devices have sensors that allow continuous measurement of physical activity, mainly through accelerometers[16].

Physical activity promotion programmes show better results when they take into account the particularities of each population. Apps and other electronic interventions therefore have been designed for focusing on promoting physical activity in different patient populations, such as people with diabetes or cancer[17,18]. However, the role played by digital medicine in the management of mental illness is more limited, despite the fact that these populations could benefit from the advantages of new technologies. Several studies demonstrate the interest shown by psychiatric patients in the use of mobile technology to improve their mental health[15,19-21]. It is therefore crucial that the large offer available on the digital market is screened by clinicians and researchers.

Nursing professionals have sown a prominent interest in e-health interventions and can play a key role in the app of new technologies to mental health care, as they are often the closest link to the patient [22]. For example, patients often prefer to ask nurses for advice on mobile apps they can use[23]. The continuous development of new technologies, however, is progressing significantly faster than the research conducted to empirically test these advances[24]. A review of the evidence on these tools is crucial to provide the best evidence-based knowledge conducive to good use of this technology. The aim of this paper is to systematically review the available evidence on mobile apps for physical activity enhancement in patients with mental illness.

MATERIALS AND METHODS

Registration

This systematic review was conducted in accordance with the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses recommendations[25]. The protocol for this systematic review was registered in the PROSPERO database (registration number: CRD42021242258).

Search strategy

We conducted a systematic literature search in the PubMed and Embase databases to identify studies on e-health interventions for the enhancement of physical activity in people with mental illness. The concept of "enhancement" encompassed both the outcomes of increased physical activity and the results obtained because of this activity (such as weight loss or improvement in other health parameters).

The inclusion criteria were as follows: (1) Original articles; (2) Published in the last ten years 10 years (November 15, 2012 to November 15, 2022); (3) Peer-reviewed journals; (4) Language: English or Spanish; (5) Exploring mobile apps for physical activity promotion in individuals with mental illness; (6) Adult population; and (7) Providing measurable outcomes, either in terms of effectiveness or feasibility.

The search terms used in PubMed were as follows: (physical[Title/Abstract] OR exercise[Title/Abstract]) AND (psychiatr*[Title/Abstract] OR mental disorder*[Title/Abstract] OR mental illness*[Title/Abstract] OR schizophreni*[Title/Abstract] OR anxiety[Title/Abstract] OR bipolar[Title/Abstract] OR depressi*[Title/Abstract]) AND (phone[Title/Abstract] OR device[Title/Abstract] OR app[Title/Abstract] OR web[Title/Abstract] OR social media[Title/Abstract] OR virtual reality[Title/Abstract] OR new technologies[Title/Abstract] OR digital[Title/Abstract] OR e-health[Title/Abstract] OR m-health[Title/Abstract]).

A similar search strategy was employed for the Embase database, such as: "(physical OR exercise) AND (psychiatr* OR mental disorder* OR mental illness* OR schizophreni* OR anxiety OR bipolar OR depressi*) AND (phone OR device OR app OR web OR social media OR virtual reality OR new technologies OR digital OR e-health OR m-health)".

Selection and extraction process

Two researchers (Guerrero-Jiménez M and Ruiz M) independently analysed the eligibility of the studies. Critical appraisal tools checklists were used to assess the quality of the articles[26]. When there was no agreement between the reviewers, the decision rested with the senior investigator. The variables of interest collected from the articles were: (1) Scientific content and technical characteristics of the apps; (2) Effectiveness; (3) Acceptability (level of approval by users); (4) Level of satisfaction; and (5) Outcome measures.

Quality assessment

Two reviewers (Guerrero-Jiménez M and Ruiz M) assessed independently the quality of the articles (this is described in Supplementary Table 1). Discrepancies between reviewers were resolved by discussing and reaching a consensus. We assessed several aspects, including methodological design, risk of bias, and reporting quality. For randomized clinical trials, Cochrane Collaboration's tool for assessing risk of bias was used.

RESULTS

Figure 1 shows the flow chart of the literature search. The initial search yielded 6257 results (PubMed = 5970; EMBASE = 302) of which 9 were finally included in the review, characteristics and main findings of the studies are recorded (Table 1)[27-35]. With the exception of two studies[28,34], the reviewed articles worked with sample sizes of less than 50 participants. All studies had positive results following intervention with mobile technologies. Acceptability was generally high, as was participation in the studies. The different studies reviewed can be divided according to the intervention tool used. Our review includes about 400 participants with different psychiatric illness as bipolar disorder and MDD.

Mobile apps

The pilot study by Macias *et al*[30] found that the use of the app promoted longer walks in obese patients with mental illness, in addition to obtaining good adherence and user satisfaction with the platform (Table 2).

Wearables

Studies such as those by Macias *et al*[30] and Naslund *et al*[31] or Aschbrenner *et al*[27] used wearables in the intervention with patients with mental illness, obtaining positive results in weight loss, and in one of the studies, improvement in physical condition.

Table 1 Characteristics and main findings of the studies

Ref.	Device	Features	Design	Sample	Measures and scales	Main findings
Aschbrenner *et al*[27], 2016	Wearable device (Fitbit Zip)	Accelerometer, step and distance registration	Pilot study pre-post	13 patients with overweight and psychiatric disorders	Satisfaction questionnaire 6-MWT; weight (kg)	At 6 mo 45% of the participants were underweight and 45% improved their physical condition
Haller *et al* [28], 2018	Internet platform	Heart rate monitor and resistance bands	RCT	20 patients with MDD (moderate and severe)	Depression scales: (1) QIDS; (2) Self-efficacy, quality of life and physical activity; and (3) General health status SF-36	Feasible and effective in patients with moderate to severe depressive symptoms, improving quality of life and decreasing depressive symptoms
Lambert *et al* [29], 2018	eMotion (Web)	Accelerometer. Weekly module course. Interactive worksheets	RCT	62 patients with at least moderate depressive symptoms and anxiety	PHQ-8. Vigorous physical activity	Depression levels were lower in the intervention group than in the control group
Macias *et al* [30], 2015	WellWave	Digital library with readings, personal messages and a variety of activities	Pilot study	10 patients with obesity and mental illness (schizophrenia, MDD or BD)	Self-assessments. Number of steps and walking time	Seven of the ten participants increased the number and duration of weekly walks. High app participation
Naslund *et al* [31], 2016	Wearable device (Fitbit Zip)	Accelerometer. Podometer. Progress Log	Prospective	34 patients with psychiatric disorders (various diagnoses)	Weight (kg). 6-MWT	Higher average daily steps were associated with greater weight loss
Naslund *et al* [32], 2016	Wearable device (Fitbit Zip)	Accelerometer. Podometer. Progress Log	Exploratory study	11 patients with severe mental illness and obesity	Quantitative usability and satisfaction questionnaire. Interviews	The use of the app motivates participants to engage in physical exercise
Naslund *et al* [33], 2018	Facebook	Messages, posting of posts, photos	Exploratory study	25 patients with mental illness (MDD, BD and schizophrenia, obesity under pharmacological treatment)	FB Interactions. 6-MWT. Weekly group attendance	Participants who actively contributed to the Facebook group have a higher weight loss
Pfirrmann *et al*[34], 2018	Web	Forum, psychoeducation	Analysis of four clinical trials	5 participants with oesophageal carcinoma, 5 with liver disease, 5 with MDD and 5 with cystic fibrosis	-	Efficacy as an exercise enhancer in all pathologies
Young and Morgan[35], 2018	SHED-IT	Measuring tape, pedometer	Pre-post study	209 male patients with overweight and depressive symptoms	PHQ-8. Weight (kg)	Reduction of weight and depressive symptoms, with a high level of engagement and satisfaction

6-MWT: 6-minute walk test; BD: Bipolar disorder; FB: Facebook; MDD: Major depressive disorder; MINI: Mini international neuropsychiatric interview; PANSS: Positive and negative syndrome scale; SCID: Structured clinical interview for axis-I DSM-IV disorders; RCT: Randomized controlled trial; PHQ: Patient health questionnaire.

Social networks

Naslund *et al*[32] explored the use of the social network Facebook in intervention with patients diagnosed with mental illness and obesity. They found that the use of this social platform prompted patients to greater motivation for weight loss, with participants with the highest number of interactions having lost the most weight.

Other digital interventions

Other studies used web-based platforms, where their effectiveness was observed, both in various pathologies[33] and in the reduction of depressive symptomatology, which was greater in the intervention group compared to the control group[28].

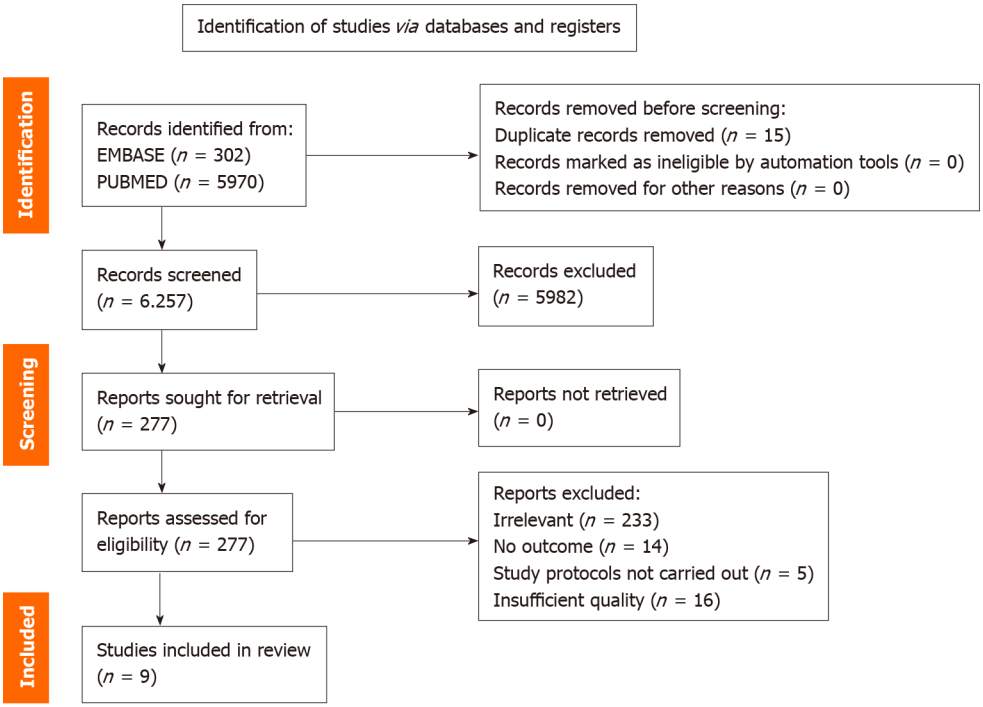
DISCUSSION

However, most of the studies focus their interventions on pathologies other than mental health, which is

Table 2 User satisfaction with the different device

Ref.	Device	Positive	Negative	Suggested improvements
Macias *et al*[30], 2015	WellWave	Personal messages, reading library	-	Test whether learning how to use the app can increase personal satisfaction
Naslund *et al* [31], 2016	Wearable device	Self-monitoring	Difficulties of use	Make tutorials on the use of the device
Naslund *et al* [32], 2016	Wearable device	Self-monitoring	Difficulties of use	Make tutorials on the use of the device. Participants are satisfied with the use of the app
Aschbrenner *et al* [27], 2016	Wearabledevice	Self-monitoring	Difficulties of use	Make tutorials on the use of the device before. High level of satisfaction
Haller *et al*[28], 2018	Web platform	Easy to use, self-monitoring	Does not include follow-up	Include monitoring as web-based apps show a trend towards non-use over time. Show a trend towards non-use over time
Lambert *et al*[29], 2018	eMotion	Self-monitoring	Not assessed	Not assessed
Naslund *et al* [33], 2018	Facebook	Accessibility, facilitates communication between people in the same condition. Allows information sharing and feedback	Not assessed	Not assessed
Pfirrmann *et al* [34], 2018	Web	Forum. Unspecific information	Not assessed	Not assessed
Young and Morgan[35], 2018	SHED-IT	Self-monitoring	Not assessed	Longer-term programme of longer duration

apps: Applications.



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Figure 1 Flow chart of the literature search.

why, despite the large amount of literature published on the subject, only 9 studies were conducted on the population to be studied and included in this review[27-35].

Discussion of effectiveness

Our findings suggest that physical exercise may be a useful tool in the management of mental disorders, and that the delivery of these interventions through e-health platforms may increase adherence and accessibility to treatment. The therapeutic effect of physical exercise can be explained by several

mechanisms. Physical activity may have neuroregenerative properties and increase brain-derived neurotrophic factor (BDNF)[36,37] although a recent meta-analysis did not find that physical exercise significantly increased BDNF in patients with depression[38].

The immune system may also be involved in this association. Inflammatory pathways are thought to play a key role in the neurobiological basis of mental illnesses such as MDD, which would explain the bidirectional association that has been found between certain mental illnesses and inflammation[39,40]. Exercise has been shown to have anti-inflammatory properties[41], and this reduction in inflammation and oxidative stress may explain the beneficial effects of exercise on mental health. This effect may be mediated by changes in the neuroimmune system, such as induction of the release of interleukin-10 and other anti-inflammatory cytokines[42,43].

Comparisons with prior reviews

Many barriers to the adoption of e-health in clinical practice remain despite the great potential of new technologies. Qualitative survey results of investigation involving patients and professionals provide some insight into the challenges that remain to be overcome for the adoption of e-health[44]. While patients appear open to using e-health, their interest differs from actual use. A 2019 survey of veterans with depression found that while 73.1% of them were interested in mental health apps, only 10.7% actually used any of them[45].

Among the most important barriers is precisely the lack of integration in public health systems, which leads to mistrust between users and professionals. In this respect, the United Kingdom is a pioneer in trying to integrate new technologies into its healthcare system[46]. Another barrier is the concern for privacy when using tools with internet access, as there is a risk of dissemination of highly sensitive data [47,48]. The absence of privacy policies is a frequent drawback when creating and using apps. Privacy is an issue of concern to users, and one of the main features they value in this type of media is that there is a method of protecting sensitive information by passwords, for example[49].

Mental disorder may act as a barrier in itself, as shown by a study in which veterans with posttraumatic stress disorder (PTSD), despite demanding more mental health services, were less willing to participate in mental health apps than their peers without PTSD[50]. The lack of confidence of medical professionals themselves in the reliability of e-health interventions sometimes slows down the adoption of mental health in clinical practice. In addition, there is a markedly smaller number of studies evaluating these interventions than the number of devices and apps available on the market[51]. Users often seek advice from their healthcare professionals, such as doctors or nurses. Training doctors, nurses and other healthcare professionals in the use of new technologies is therefore a crucial element in accelerating the adoption of these interventions in clinical practice[52,53].

CONCLUSION

Digital medicine represents a tool of great potential in clinical practice. Thanks to their great versatility and acceptance among users, new technologies can open up new fields in mental health care. In the specific case of physical exercise enhancement in mental health patients, new technologies can facilitate adherence to exercise programmes and increase their personalization. However, there are still wide-ranging barriers to the adoption of these interventions on a day-to-day basis. One of the steps needed to advance research is the development of new apps and tools, and their testing in exploratory articles with larger sample sizes.

Another of the fronts to be explored is the field known as machine learning. From the huge amount of data that these devices can collect, we can detect behavioural patterns characteristic of each person and thus optimise interventions to individual needs. This is a step towards participatory medicine, a paradigm shift that has been pursued for years[53], in which the integration of multidisciplinary treatment teams would also be an important point.

ARTICLE HIGHLIGHTS

Research background

Mobile applications (apps) have proven to be very useful in improving physical health in numerous medical illnesses.

Research motivation

We want to know if apps have proven to be useful in patients with mental illness.

Research objectives

The main objective of the present systematic review is to know the efficacy of apps to increase physical

activity in patients suffering from mental illness.

Research methods

We have carried out a systematic review, following the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses recommendations, of the last 10 years, selecting articles that have studied the efficacy of apps in increasing physical activity in patients with mental illness. The quality of the selected studies was also analyzed.

Research results

From 6257 initial articles we included finally 9 articles that met the criteria for inclusion. We resume the principal studies that have showed an improvement in reduction of weight and depressive symptoms and an increase of level of satisfaction and physical exercise in patients that are suffering a mental disease.

Research conclusions

Apps can be a good strategy to improve the physical health of patients with mental illness.

Research perspectives

In the future, digital tools should be developed to analyze clinical efficacy using multivariate analysis, larger samples, including different psychiatric diseases and more specific treatments using artificial intelligence (machine learning).

FOOTNOTES

Author contributions: Guerrero-Jiménez M and Ruiz M contributed equally to this work; Gutiérrez-Rojas L, Jiménez-Muñoz L, Baca-Garcia E and Porras-Segovia A designed the research study; Ruiz M, Jiménez-Muñoz L and Porras-Segovia A performed the research; Guerrero-Jiménez M and Ruiz M contributed analytic tools; Guerrero-Jiménez M, Ruiz M, Gutiérrez-Rojas L and Porras-Segovia A analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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SYSTEMATIC REVIEWS

COVID-19 pandemic in the intensive care unit: Psychological implications and interventions, a systematic review

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic produced changes in intensive care units (ICUs) in patient care and health organizations. The pandemic event increased patients' risk of developing psychological symptoms during and after hospitalisation. These consequences also affected those family members who could not access the hospital. In addition, the initial lack of knowledge about the virus and its management, the climate of fear and uncertainty, the increased workload and the risk of becoming infected and being contagious, had a strong impact on healthcare staff and organizations. This highlighted the importance of interventions aimed at providing psychological support to ICUs, involving patients, their relatives, and the staff; this might involve the reorganisation of the daily routine and rearrangement of ICU staff duties.

AIM

To conduct a systematic review of psychological issues in ICUs during the COVID-19 pandemic involving patients, their relatives, and ICU staff.

METHODS

We investigated the PubMed and the ClinicalTrials.gov databases and found 65 eligible articles, upon which we commented.

RESULTS

Our results point to increased perceived stress and psychological distress in staff, patients and their relatives and increased worry for being infected with severe acute respiratory syndrome coronavirus-2 in patients and relatives. Furthermore, promising results were obtained for some psychological programmes aiming at improving psychological measures in all ICU categories.

CONCLUSION

As the pandemic limited direct inter-individual interactions, the role of interventions using digital tools and virtual reality is becoming increasingly important. All considered, our results indicate an essential role for psychologists in ICUs.

Key Words: COVID-19; Intensive care unit; Psychological interventions; Pandemic; Mental health; Health care professionals

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic produced changes in patient care and organization of intensive care units (ICUs). The pandemic event increased patients' risk of developing psychological symptoms during and after hospitalisation. We carried out a systematic review of the psychological issues raised in ICUs during the COVID-19 pandemic which concerned patients, their relatives, and the ICU staff. Our results point to increased perceived stress and psychological distress in staff, patients and their relatives and increased worry for being infected with severe acute respiratory syndrome coronavirus-2 in patients and relatives. Promising results were obtained for some psychological programmes and interventions using digital tools and virtual reality aiming at improving psychological measures in all ICU categories.

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INTRODUCTION

Intensive care unit (ICU) utilisation during the coronavirus disease 2019 (COVID-19) pandemic accounted for around 25% of patients hospitalised during the February 2020 to September 2021 period in 21 United States Healthcare systems[1]. The COVID-19 pandemic has produced changes in ICUs both in patient care and in hospital care organization. On the one hand, the high burden of stress that patients usually experience in the ICU, has been exacerbated by the fear of the virus and the need to isolate, especially from family members. The pandemic has consequently increased the patient's risk of developing important psychological symptoms during and after hospitalization[2-4]. In addition, family members also experienced psychological symptoms due to the lack of access to the hospital, as this keeps them away from their loved ones and made it more difficult to exchange information with health workers[5]. Psychological symptoms associated with the COVID-19 pandemic, despite being more severe in the patient population, match those of relatives[6]. Finally, the lack of knowledge about the virus and its management, the climate of fear and uncertainty, increased workload, and the risk of becoming infected and infecting loved ones, had a great impact on staff[7-9]. This highlighted the importance of interventions aiming to provide psychological support to the treatment team, to reorganise the daily routine, and to characterise the role of the professionals working in an ICU.

With the awareness that the COVID-19 emergency is not over, the aim of this review was to highlight the changes and developments occurring in ICUs during the pandemic, knowing that many of its characteristics and changes are still important and will probably be in the future. The need to monitor the psychological phenomena taking place in ICUs during the COVID-19 period and to implement adequate interventions in the same structures has already been stressed in neonatal/paediatric[9,10-13] and adult age[14]. A review focused on the role of the psychologist in paediatric ICUs[15], and other two in adults were systematic reviews, one on informational and educational interventions in ICUs[16], the other on bereavement support[17], while one study identified three areas of utility of a psychologist in an ICU, namely, attention to patients at the ICU, attention to family members or caregivers, and work with health personnel[18]. There are currently no studies collecting experiences and evidence of effectiveness of psychological interventions during the COVID-19 pandemic. Hence, through this review we intend to investigate the psychological characteristics of ICU admission during the pandemic, through the assessment of the perspectives of the various involved individuals, *i.e.*, patients, family members, and staff members, and on the interventions that the psychologist, along with the medical team, enforced to deal with the health emergency.

We will start by describing patients' most frequent psychological repercussions of ICU admission and stay. Subsequently, we will summarise the elements of the main psychological characteristics of patients, family members, and caregivers during the COVID-19 pandemic.

As the pandemic limited direct, person-to-person interindividual interactions, with a concomitant rise in the use of digital homework, we found it interesting to dedicate a section of this review to interventions with digital tools. During the pandemic, these tools proved to be very effective (besides being the only available) in facilitating communication at various levels. Within this framework, we also highlight the role of virtual reality (VR) used in intensive care to treat the psychological consequences and promote the well-being of patients hospitalised with COVID-19 (and their relatives).

MATERIALS AND METHODS

To identify evidence of psychological issues and interventions in ICUs, we searched the PubMed database adopting the following search strategy: COVID-19 AND ("Intensive Care Unit" OR ICU) AND psychol* AND (implicat* OR intervent*), which produced on September 30, 2022, 214 results. We also searched the ClinicalTrials.gov database using the strategy Condition or disease: COVID-19 and Other terms: intensive care unit AND psychological, which produced 41 results on the same date. Eligibility depended on being an experimental work having data, either epidemiological or interventional. Excluded were reviews (and meta-analyses as well as guidelines; n = 25), case reports and series (n = 5), opinion articles (n = 16, editorials, comments on other articles, and reports without data), protocols of future studies (n = 17), articles not reporting on psychological outcomes or interventions, not involving ICUs, or not involving COVID-9 (collectively labelled as outcome, n = 52), studies not providing results (n = 38), studies lumping ICU data with data from other wards without providing separate data for ICUs (n = 6), studies with overlapping populations (n = 1, in which case only the article with the higher sample size would have been selected, provided it was higher in quality than others), studies with inadequate design to obtain the desired results (n = 16), unfocused articles (n = 12), papers unrelated to the subject matter (n = 5), *post mortem* studies (n = 0), and animal studies (n = 0).

RESULTS

Reviews/meta-analyses and guidelines were excluded but we thoroughly searched their reference lists for studies that possibly eluded our database searches. Duplicates were also to exclude if occurring in both searched databases (n = 0). When adding records concerning ClinicalTrials.gov to those of PubMed, we took care to substitute those that had their NCT number published within PubMed with the published article and rate it as appropriately. One ClinicalTrials.gov record produced four additional articles published with its NCT number, thus amounting to a grand total of 259 records. ClinicalTrials.gov added 1 eligible article; the 64 identified by PubMed. PubMed results did not overlap with those of ClinicalTrials.gov. We found no duplicates in our searches. Of the records identified by our ClinicalTrials.gov search, 19 were completed, but only 1 of them had results (and was not eligible, record 29 in Supplementary Material), 9 were still recruiting, 7 were active, but not recruiting, 1 was not yet recruiting, 3 had unknown status, and 2 were terminated (one in Malaysia for logistical problems/administrative issues, the other in Turkey, due to technical reasons). Most projects were based in France (n = 19, 1 in its extra-European territories), other 9 in Northern Europe and British isles (5 Belgium, 2 the Netherlands, 1 Denmark, and 1 United Kingdom), 6 in Southern Europe (3 Spain, 2 Turkey, and 1 Italy), 5 in the Americas (3 United States, 1 Brazil, and 1 Colombia), 1 in Asia (Malaysia), and 1 in Africa (Egypt) (Supplementary Material). The first was first-posted on June 19, 2019, the last on June 16, 2022, indicating early and enduring interest in the subject. Qualitative analyses were included if they adequately assessed psychological outcomes, but unfortunately, most did not. We assessed eligibility by reaching consensus among five authors (Monti L, Tranquilli S, Mazza M, Marconi E, and Kotzalidis GD) through Delphi rounds; no more than two were necessary to establish it. The results of the search are shown in Figure 1[19]. The list of studies considered is in the Supplementary Material in a Table, where reasons for exclusion are provided for each study (Supplementary Material). The final number of included studies was 65, spanning from July 2, 2020 to September 23, 2022. A summary of their results is provided in Table 1.

DISCUSSION

Psychological implications of being hospitalised in an ICU: ICU admission

Admission to the ICU often has significant consequences for patients and their caregivers and family members[20]. It is an event with traumatic potential. In fact, it involves a high stress charge due to invasive and painful procedures, sleep deprivation, unnatural noises and lights, inability to communicate, feeling of helplessness, and especially imminent threat of death[21]. The most frequent negative experiences reported by patients were thirst, loss of control, and noise[22].

During the COVID-19 pandemic, patients reported increased stress, probably related to the increased preventive and personal protective measures and the increased isolation from family, friends, and caregivers[20]. Indeed, many patients recall traumatic and loneliness elements in their ICU experience and many of them were admitted to the ICU during the pandemic while family members were in critical, sometimes fatal, conditions[23]. ICU admission often renders patients psychologically vulnerable; in fact, patients frequently report high levels of anxiety and depression[24]. Such symptoms may affect treatment plans and outcomes[25]. Psychological distress and psychiatric symptoms should be taken into account to prevent worsening of the quality of life after leaving the ICU[26].

Psychological implications of being hospitalised in an ICU: During ICU hospital stay

People who are admitted to ICUs may already have or not have psychological distress; ICU admission may worsen pre-existing psychological distressed, expressed as a variety of psychiatric symptoms which resemble post-traumatic stress disorder (PTSD), depression, excessive worrying, insomnia, and anxiety, or may induce newly developed psychological distress. An Italian study found that ICU admission may be associated with increased depression levels and suicidal ideation in a small, but clinically significant proportion of patients with COVID-19, and may worsen pre-existing depression [27]. A Turkish study showed depression may be mediated by restricted visits to the ICU patient, while anxiety was mediated by ICU admission itself[28]. In this study, ICU admission and visit restriction were independent risk factors; positive polymerase chain reaction for COVID-19 and female gender were associated with both anxiety and depression, as assessed with the Hospital Anxiety and Depression (HAD) scale. Another Turkish study examined the quality of sleep using the Pittsburgh Sleep Quality Index and depression and anxiety with the HAD in ICU patients with COVID-19; poor sleep quality was associated with depression and longer ICU hospitalisation[29]. The authors concluded that through improving sleep quality would help reducing duration of ICU stay.

Clozapine is a second-generation antipsychotic agent that is reserved to severe, treatment-resistant cases of schizophrenia and bipolar disorder due to potentially life-threatening agranulocytosis. Because of this, it is associated with worse pulmonary outcomes, namely pneumonia[30]. Although the use of second-generation antipsychotics is generally associated with reduced odds of getting a COVID-19 infection[31], it has been suggested that patients on clozapine may be at higher risk of COVID-19

Table 1 Summary of eligible studies on coronavirus disease 2019 in intensive care units

Ref.	Type	Population	Design	Outcomes and assessments	Results	Conclusions and observations
Sayde *et al* [138], 2020	C-S survey	265 ICU patients recruited, 20 refused, 185 excluded, 35 included: 17: Intervention group, (16 female, 11 male); 18 patients control group (15 female,13 male)	Diary and questionnaire administered 1 (BL), 4, 12, and 24 wk after ICU discharge (September 2017 to September 2018) in New Orleans, Louisiana, United States	Psychological distress, (IES-R), Anxiety and Depression (PHQ-8; HADS; GAD-7)	Controls had a significantly greater decrease in PTSD, hyperarousal, and depression symptoms at week 4 compared to the intervention group. No significant differences in other measures, or at other follow-ups. Both study groups exhibited clinically significant PTSD symptoms at all timepoints after ICU discharge	Diary increased awareness of the psychological support available to ICU survivors and family members
Huang *et al* [139], 2020	C-S online survey	6523 people with contact history, completed the survey, 260 were excluded, 6261 included. 3585 female (57.3%), 2676 male (42.7%)	Online questionnaire sent to participants of Hubei province and outside Hubei province, China, from February 10 to 15, 2020	Tested depression (PHQ-9) and public perceptions in response to the COVID-19 outbreak	Most people endorsed preventive and avoidance behaviours. People from Hubei, with contact history, and people who were infected or whose family members were infected by COVID-19, had a much higher prevalence of depression and anxiety	Assessing public response, perception, and psychological burden during the outbreak may help improving public health recommend-ations and deliver timely psychological intervention
Leng *et al*[140], 2021	C-S survey	90 ICU nurses; 65 female (72.2%), 25 male (27.8%)	Tests administered to ICU Wuhan (China) nurses, from 11 to 18 March 2020	PTSD (PTSD Checklist-Civilian and PSS), related to demographic survey and 2 open questions	Nurses have elevated PTSD levels. Nurses' stress and PTSD symptoms were positively correlated. Isolated environment, concerns about personal protective equipment shortage and usage, physical and emotional exhaustion, intensive workload, fear of being infected, and insufficient work experiences with COVID-19 were a major stress source	Even highly skilled and resilient nurses experienced some degree of mental distress, such as PTSD symptoms and perceived stress
Lasater *et al* [80], 2021	C-S analyses	ICU nurses and ICU patients: First sample 4298 medical-surgical nurses; second sample 2182 ICU nurses	Staffing data collected from registered nurses in New York and Illinois using HCAHPS and AHA, between 16-12-2019–24-2-2020	Information on patient satisfaction, hospital characteristics	Over half the nurses experienced high burnout. Half gave their hospitals unfavourable safety grades and two-thirds would not definitely recommend their hospitals. One-third of patients rated their hospitals less than excellent and would not definitely recommend it to others	Hospital nurses had burn-out and were working in understaffed conditions in the weeks prior to the first wave of COVID-19 cases, thus increasing public health risks
Jain *et al*[81], 2020	C-S online survey	512 Indian anaesthesiologists, 227 female (44.3%), 285 male (55.7%)	Online questionnaire sent to anaesthesi-ologists across India from 12-5-2020 to 22-5-2020	Anxiety (GAD-7) and Insomnia (ISI)	Elevated COVID-19-related anxiety and insomnia levels of anaesthesiologists. Age < 35 yr, female sex, being married, resident doctors, fear of infection to self or family, fear of salary deductions, increase in working hours, loneliness due to isolation, food and	Anaesthesiologists on COVID-19 duty suffer from anxiety and insomnia

					accommodation issues and posting in COVID-19 duty were risk factors for anxiety. < 35 yr, unmarried, those with stress due to COVID-19, fear of loneliness, issues of food and accommodation, increased working hours favour insomnia	
Kirolos *et al* [82], 2021	LS	41 families with a baby at NICU	Multicentre service evaluation in five United Kingdom neonatal care units, between July and November 2019	Surveys contained quantitative (9-point Likert scale, or closed-ended yes/no responses) and qualitative items (open comment boxes)	In post-implementation surveys (n = 42), 88% perceived a benefit of the service on their neonatal experience. 71% (n = 55) felt the service had a positive impact on relationships with families	Asynchronous video supports models of family integrated care and can mitigate family separation
Lasalvia *et al* [83], 2020	C-S online survey	2195 ICU HCWs; female 539 (24.7 %), male 1647 (75.3)	All healthcare and administrative staff of Verona University Hospital (Veneto, Italy) from April to May 2020	Psychological distress (IES-R), Anxiety (SAS) and mental health (PHQ-9)	63.2% of participants reported COVID-related traumatic experiences at work; 53.8% showed symptoms of post-traumatic distress; 50.1% showed symptoms of clinically relevant anxiety; 26.6% symptoms of moderate depression	The psychological impact of the COVID-19 pandemic on healthcare staff working in a highly burdened north-east Italy is high and to some extent higher than that reported in China
Ou *et al*[84], 2021	C-S study	92 nurses in isolation ward, female 85 (92.4%); male 7 (7.6%)	Test was administered to nurses in isolation ward, the Guangdong Province of China, in February 2020	Resilience and psycho-pathological symptoms (CD-RISC2; SCL-90)	Total resilience score was 87.04 ± 22.78. SCL-90 score ranged 160-281 (202.5 ± 40.79). Only 8.70% of nurses (n = 8) scored > 160 on the SCL-90, suggesting positive symptoms. Most nurses had 0 to 90 positive self-assessment items (median 14); 19.57% (n = 18) had > 43 positive items to CD-RISC 2	High resilience promotes physical and mental health, and may be improved by training, psycho-logical interventions, and full use of hospital resources
Vlake *et al*[69], 2020	Case report	One COVID-19 patient (male), age: 57 yr	Test for evaluating COVID-19 ICU-VR intervention in one Dutch man with COVID-19	Anxiety and depression (HADS) and psycho-logical distress (IES-R)	One week after receiving ICU-VR, levels of PTSD, anxiety, and depression had normalised and stayed normal 6 mo after discharge	Virtual realty improved psycho-logical rehabilitation outcomes, hence they should be considered by clinicians for the treatment of ICU-related psychological sequelae after COVID-19
Fernández-Castillo *et al* [85], 2021	C-S survey	17 nurses: 6 male, 11 male	17 nurses of a tertiary teaching hospital in Southern Spain, from 12-30 April 2020	Semi-structured videocall interviews	Four main themes emerged from the analysis and 13 subthemes: "providing nursing care", "psychosocial aspects and emotional lability", "resources management and safety" and "profes-sional relationships and fellowship"	Nursing care has been influenced by fear and isolation, making it hard to maintain humanisation of health care
Writing Committee for the COMEBAC Study Group *et al*[86], 2021	C-S telephone survey	834 eligible COVID-19 survivors: 478 evaluated (201 male, 277 female)	Survivors of COVID-19 in France underwent telephone assessment 4 mo after discharge, between July and September 2020	Respiratory, cognitive, and functional symptoms (Q3PC cognitive screening questionnaire, symptom Checklist and 20-item Multidimensional	244 patients (51%) declared at least 1 symptom absent before COVID-19: Fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnoea in	4 mo after hospital-isation for COVID-19, a cohort of patients frequently reported previously absent symptoms

				Fatigue Inventory; SF-36; cognitive impairment (MoCA)	16%. The median 20-item Multidimensional Fatigue Inventory score (n = 130) was 4.5 for reduced motivation and 3.7 for mental fatigue. The median SF-36 score (n = 145) was 25 for the subscale "role limited owing to physical problems". Among 94 former ICU patients, anxiety, depression, and PTSD symptoms were observed in 23%, 18%, and 7%, respectively. The left ventricular ejection fraction was < 50% in 8 of 83 ICU patients (10%)	
Stocchetti *et al* [87], 2021	C-S online study	Of 271 medical staff working in this ICU, 136 included: 84 nurses (62%) and 52 physicians (38%)	Nurses and physicians working in this ICU participated to online survey in January 2021	Burnout (MBI), anxiety (HADS); resilience (RSA) and Insomnia (ISI)	60% of participants show high burnout level: Nurses reported significantly higher scores of anxiety and insomnia levels. 45 % reported symptoms of depression, and 82.4% of the staff showed moderate-to-high levels of resilience	The COVID-19 pandemic can have a significant impact on ICU staff. Effective interventions needed to maintain healthcare professionals' mental health and relieve burnout
Kirk *et al*[12], 2021	C-S online study	430 of 458 paediatric HCWs, concluded the online survey	Online survey administered to paediatric HCWs in the emergency, ICU and infectious disease units from April 28 to May 5 2020	Depression and Anxiety symptoms (DASS-21)	168 (39.1%) of respondent showed depression, 205 (47.7%) anxiety and 106 (24.7%) symptoms of stress. Depression reported in the mild (47, 10.9%), moderate (76, 17.7%), severe (23, 5.3%) and extremely severe (22, 5.1%) categories. Anxiety (205, 47.7%) and stress (106, 24.7%) were reported in the mild category only	A high prevalence of depression, anxiety and stress was reported among frontline paediatric HCWs during the COVID-19 pandemic
Yang *et al*[88], 2021	C-S online study	Of 1075 contacted individuals, 1036 front-line HPCD completed the online survey: Female 755 (72.9%), male 288 (27.1). 874 (84.4%) nurses, 162 (15.6%) physicians	1036 front-line HPCDs exposed to COVID-19 were tested online from 5 to 9 March 2020 in Wuhan, China	Sleep, insomnia, emotional regulation (RESE)	543 (52.4 %) reported symptoms of sleep disorders. HPCD for patients with COVID-19 in China reported experiencing sleep disturbance burdens, especially those having exposure experience and working long shifts	RESE is an important resource for alleviating sleep disturbances and improving sleep quality
Moradi *et al* [89], 2021	C-S survey	17 nurses in ICUs: 5 males and 12 females	Semi-structured face-to-face interviews were administered to nurses in ICUs of Urmia, Iran	Semi-structured face-to-face interviews	Four challenges throughout the provision of care for COVID-19 patients: 'organization's inefficiency in supporting nurses', 'physical exhaustion', 'living with uncertainty' and 'psychological burden of the disease	A profound understanding of ICU nurses' challenges while caring for COVID-19 patients is needed to increase healthcare quality
Bruyneel *et al* [90], 2021	C-S online survey	1135 ICU nurses: Female 892 (78%); male 243 (22%)	Nurses in the French-speaking part of Belgium completed a web-based survey, April 21-May 4, 2020	Burnout (MBI)	68% burnout level. 29% of ICU nurses were at risk of depersonalisation, 31% of reduced personal accomplishment, and 38% of emotional exhaustion	Burnout risk requires monitoring and implementation of interventions to prevent it and manage it

Shariati *et al* [91], 2021	LS online survey	67 family members of COVID-19 patients admitted to the ICU	Longitudinal pre-post intervention online survey of 67 family members of COVID-19 ICU patients in three hospitals in Iran; May to August 2020	Stress symptoms (PSS-14)	Mean PSS-14 post-intervention significantly lower in the intervention group than in the control group ($P < 0.001$)	Use of web-based communication between nurses and family members was effective in reducing perceived stress
Kok *et al*[92], 2021	LS survey	Open cohort of ICUs professional: BL survey 252 respondents, response rate: 53%, male 66 (26.2%), female 186 (73.8%); and follow-up 233 respondents, response rate: 50%, male 65 (27.9%), female 168 (72.1%)	BL survey collected in October-December 2019 and follow-up survey sent in May-June 2020 to a university medical centre and a large teaching hospital in the Netherlands	Semi-structured interview form	The prevalence of burnout symptoms was 23.0% before COVID-19 and 36.1% after, with higher rates in nurses (38.0%) than in physicians (28.6%). Post-COVID-19 incidence rate of new burnout cases among physicians was higher (26.7%) than among nurses (21.9%). Higher prevalence of burnout symptoms after the beginning of the pandemic	Overburdening of ICU healthcare personnel during an extended period leads to burnout symptoms
Kürtüncü *et al* [93], 2021	C-S survey	18 COVID-19 patients: 4 females and 14 males	Telephone-conducted semi-structured interview of 18 ICU patients in Turkey; March-September, 2020	Semi-structured interview form	Interventions in ICUs are able to promote communication with patients and are essential for achieving positive circumstances	Families of missing patients may benefit from interventions of nurses aimed at working-through the loss and providing family support and care during their critical illness
Martillo *et al* [94], 2021	C-S online survey	45 COVID-19 ICU patients: Male 33 (73.3%), female 10 (22.2%)	Single-centre descriptive cohort study of ICU patients at Mount Sinai Hospital, New York; April 21 to July 7, 2020	Insomnia (ISI), mental health (PHQ-9), QoL (EQ-5D-3L), PTSD (PCL-5), telephone cognitive assessment (MoCA)	22 patients (48%) reported psychiatric impairment, and four (8%) had cognitive impairment. 38% at least mild depression, and 18% moderate-to-severe depression. 8% PTSD. 9% had impaired cognition	Severe COVID-19-related symptoms associated with high risk of developing PICS. Planning needed for appropriate post-ICU care
Donkers *et al* [95], 2021	C-S online survey	355 nurses, 108 supporting staff and 41 ICU physicians from 84 ICUs: 124 males, 380 females	Online questionnaire sent by email to Dutch ICU nurses and supporting staff from 7 April to 11 June, 2020	MD for HCWs (MMD-HP), Ethical Decision-Making (EDMCQ)	MD levels higher for nurses than others; "Inadequate emotional support for patients and their families" was the highest-ranked cause of MD for all participants; all participants judged positively the ethical climate regarding the culture of mutual respect, ethical awareness, and support	Targeted interventions on MD are important for improving the mental health of critical care professionals and the quality of patient care
Fteropoulli *et al* [96], 2021	C-S online survey	1071 healthcare personnel: 73% females, and 27% males	Anonymous online survey administered. May 25 to October 27, 2020, in Cyprus	QoL (WHOQOL-Brief), anxiety (GAD-7), depression (PHQ-8), burnout (CBI), and coping (Brief COPE)	27.6% moderate and severe anxiety, 26.8% depression. Being female, nurse or doctor, working in frontline units, perceptions of inadequate workplace preparation to deal with the pandemic and using avoidance coping were risk factors	There are several risk factors for psychological distress during the pandemic, which may be individual, psychosocial, and organisational
Peñacoba *et al* [97], 2021	C-S online survey	308 intensive care nurses: Female 268 (87%) and male 40 (13%)	Online form used to collect data from surgical and general critical care units in a public Spain Hospital, March 2020 to June 2020	Stress subscale (depression, anxiety, and stress in Spanish DASS-21), physical and mental health-related QoL (SF-36), GSES, and resilience (RS-14)	Greater perception of self-efficacy related to lower perception of stress and greater resilience, while higher resilience was linked to greater physical and	Stress is related to physical and mental health factors which are linked to QoL through self-efficacy and resilience

					mental health	
Wozniak *et al* [98], 2021	C-S online study	3461 HCWs of 352 ICU	Online data collected from May 28 to July 7, 2020, at HUG, Switzerland	Socio-demographic data, lifestyle changes, anxiety (GAD-7; PHQ-9), psychological distress (PDI; WHO-5)	145 (41%) reported poor well-being, 162 (46%) anxiety, 163 (46%) depression, 76 (22%) peritraumatic distress. Working in ICU more than other departments changes eating habits, sleeping patterns, and alcohol consumption ($P < 0.01$)	High prevalence of anxiety, depression, peritraumatic distress and poor well-being during the first COVID-19 wave among HCWs, especially in ICU
Li *et al*[99], 2021	C-S survey	78 ICUs nurses: Female 4 (17.95%), male 64 (82.05%)	Data from 78 ICU nurses in Beijing COVID-19 hospital during March 2020	Depression (SDS), stress (PPS)	44.9% ($n = 35$) reported depressive symptoms, stress perception; work experience in critical diseases, and education are risk factors for depression	Work experience in critical illness is linked to depression. Psychological intervention may reduce it
Manuela *et al* [100], 2021	C-S survey	34 females, mothers of premature infants born before 32 wk of gestational age; 20 pre-COVID-19 period *vs* 14 during COVID-19 pandemic	20 mothers of premature infants recruited at HUG, CH, January 2018 to February 2020 before COVID-19 *vs* 14 mothers from November 2020 to June 2021	Postnatal depression (EPDS); (PSS:NICU), attachment (MPAS)	No significant differences for depression, stress, and attachment between the two groups; "trend" towards increase of depression symptoms in mothers during the COVID-19 pandemic; depression correlated with attachment and stress scores	Protective family-based actions and appropriate interventions to support parents during the COVID-19 pandemic can reduce depression and stress of mothers of premature infants
Nijland *et al* [76], 2021	LS survey	Of 326 ICU nurses, 138 (42.33%) participated; 86 VRelax users, male 13 (15%), female 73 (85%) and 52 non-users, male 9 (17%), female 43 (83%)	VRelax intervention investigated in Dutch ICU nurses in May, 2020	Single-question VAS-stress scale	VR reduced stress by 36% (mean difference = 14.0 ± 13.3, $P < 0.005$). 62% of ICU nurses rated VRelax as helpful to reduce stress	VRelax is effective in reducing immediate perceived stress
Scheepers *et al* [101], 2021	LS survey	Of 203 ICU and internal medicine staff, 103 residents (50.1%) participated	ICU and Internal medicine staff of AMC, Amsterdam, The Netherlands tested during the first wave of COVID-19, March 15 to June 30, 2020	Explored residents' perceptions of well-being (well-being survey), and their perceived support of the well-being program during the COVID-19 pandemic	Residents working in the ICU reported significantly lower levels of mental well-being than internal medicine residents	Well-being programmes for ICU staff need to address ICU-specific stressors, enhancing supervision and peer support
Liu *et al*[102], 2021	Study 1: LS survey; study 2: LS survey	Study 1: Of 268 ICU nurses and 26 head nurses, 258 completed the survey: Female 220 (85.27%), male 38 (14.73%). Study 2: 64 ICU medical professionals: Female 40 (65.57%), male 24 (34.43%)	Study 1: ICU nurses of major Chengdu hospital, China, recruited. Retested after 3 wk for work engagement and rated by head nurses for taking-charge behaviour after further 3 wk. Study 2: ICU medical staff of same Chinese hospital completed scales on early March, 2020 and 2 wk later	Studies 1-2: Perceived COVID-19 crisis strength and work meaningfulness assessed with 5-point Likert scales, and demographic data. Self-rating of work engagement and clinician rating of taking-charge behaviour	Study 1: Health worker'sperceived COVID-19 crisis strength exerted a more negative effect on his or her work engagement and taking charge at work. Study 2: The interventions significantly decreased perceived COVID-19 crisis strength and increased work meaningfulness for medical staff in an ICU	Study 1: Frontline health workers worldwide have regarded the COVID-19 crisis as an extraordinarily stressful event. Study 2: Interventions are important for reducing stress during COVID-19 pandemic
Carmassi *et al* [103], 2021	C-S survey	265 frontline HCWs: Male 84 (31.7%), female 181 (68.3%)	Data was recruited in a sample of frontline HCWs at a major university hospital in Pisa, Italy, April 1 to May 1, 2020	PTSS (IES-R), anxiety (GAD-7), depression (PHQ-9), assess work and social Functioning (WSAS)	Subjects with acute PTSS have higher levels of PTSS, depressive symptoms, and moderate-to-severe anxiety symptoms	More long-term studies are needed to evaluate the impact of psychopathology on the socio-occupational functioning of health professionals
Secosan *et al* [104], 2021	C-S survey	Of 200 frontline HCWs, 126, 63% (32 nurses and 94 physicians)	Data collected from Romanian frontline HCWs, March to April 2020	Psychological capital (PsyCap) (PCQ) related to anxiety and depression (DASS-21),	High anxiety predicts lower emotional exhaustion and a low level of mental health	PsyCap is may decrease the impact of anxiety and depression on

		participated; male 35.7%, female 64.3%; 42.8% single, 52.3% married, 4.7% divorced		burnout (MBI)	complaints about healthcare professionals when PsyCap is high	psychological outcomes in frontline HCWs. Psychological interventions can help ICUs staff
Scarpina *et al* [105], 2021	C-S survey	60 patients who survived COVID-19 infection: Male 58.3%, female 41.7%	Participants had been recruited at the COVID-19 post-ICU, from May 2020 to January 2021, in Italy	Fearful facial expressions recognition, perceived psychological functioning, Empathy (4-point Likert scale questionnaire)	Altered detection and recognition of fearful expressions and altered processing of fearful expressions in individuals who survived COVID-19 infection	Altered emotional face recognition could represent psychological distress; psychological interventions in rehabilitative settings can be helpful
Kapetanos *et al* [106], 2021	C-S survey	381 HCWs: 72.7% nurses (202 males, 75 males) 12.9% physicians (28 males, 21 males), 14.4% other occupations (18 males; 7 males)	Data on mental health status of HCWs collected from healthcare professionals from all over Cyprus from May to June 2020	64-item, self-administered questionnaire, which included DASS21 and MBI	Prevalence of 28.6% anxiety, 8.11% stress, 15% depression, and 12.3% burnout. Environmental changes included increased working hours, isolation, and separation from family	Also the second wave of the pandemic impaired psychological health of HCWs
Manera *et al* [107], 2022	C-S survey	152 COVID-19 patients: 101 males, 51 females	Retrospective assessment of post-infectious SARS-CoV-2 patients at Maugeri Scientific Clinical Institutes, Northern Italy, May 2020 to May 2021	Cognitive measures (MMSE) as related to disease severity (at-risk *vs* not at-risk: Neuro+ *vs* Neuro-)	Mild-to-moderate patients (26.3%) showed impaired MMSE performances; ICU patients made less errors (P = 0.021) on the MMSE than non-ICU patients. Age negatively influenced MMSE performance. For Neuro-patients, steroidal treatment improved MMSE scores (P = 0.025)	Mild-to-moderate patients, with mechanical ventilation who however are not admitted to an ICU, are more likely to suffer from cognitive deficits, independently from their aetiology
Mollard *et al* [108], 2021	C-S survey	885 postpartum women, 82.3% married	English-speaking adult postpartum women who gave birth in US hospitals from 1 March to 9 July 2020 participated in survey between 22 May to 22 July 2020	Demographic and health variables measured with self-report questionnaires; stress (PSS-10), Mastery (PM), and resilience (CD-RISC2)	Post-pandemic participants showed higher stress and lower resilience, high levels of depression, anxiety, and stress compared to a pre-pandemic normative sample. Women with an infant admitted to a NICU had higher stress. High income, full-time employment, and partnered relationships lowered stress. Lower stress increased mastery and resilience. Non-white women showed higher stress and lower resilience	Postpartum women are susceptible to stress, depression, and anxiety
Pappa *et al* [109], 2021	C-S survey	464 HCWs: Female 68%, male 32%; 43% nurses, 49% married	Six COVID-19 reference hospitals in Greece, from May 2020 to June 2020	Levels and risk factors of anxiety (GAD-7), Depression (PHQ-9), traumatic stress (IES-R), burnout (MBI) and fear (NFRS)	30% moderate/severe depression, 25% anxiety, 33% traumatic stress. 65% of respondents scored moderate-severe on EE, 92% severe on DP, and 51% low-moderate on PA. Predictors: Fear, perceived stress, risk of infection, lack of protective equipment and low social support	Need for immediate organisational and individual interventions to enhance resilience and psychological support for HCWs
Meesters *et al* [110], 2022	C-S online survey	25 parents (16 mothers, 9 fathers) of infants at NICU	Data collected at Rotterdam NICU from April to June 2020	Sociodemographic questions related to stressor (PSS:NICU) and COVID questionnaire	Most important sources of stress were being separated from, not being able to always hold their infant, and other family members	NICU staff can support psychologically parents during hospital isolation and reduce the effect of

					not allowed to visit	restrictive measures
Piscitello *et al* [111], 2022	LS survey	Of 78 eligible, 33 ICU nurses (42%) completed survey: Female 29 (50.9%), male 28 (49.1)	Data collected November to December 2020 at Rush University	Nurse MD (MMD-HP)	Results pre and post intervention were not statistically different	Further research required to identify interventions that could improve nurses' MD
Sezgin *et al* [112], 2022	C-S online survey	10 ICU nurses: 2 males and 8 females	Data collected by online survey in 10 ICUs of 7 hospitals in İstanbul, Turkey, October to December 2020 using the snowball method to recruit	Followed the Consolidated Criteria for Reporting Qualitative Research; 32-item checklist to identify major themes	'Death and fear of death', 'impact on family and social lives', 'nursing care of COVID-19 patients', 'changing perceptions of their own profession: empowerment and dissatisfaction', and 'experiences and perceptions of personal protective equipment and other control measures' are the major themes identified	There is need to improve working conditions and develop nursing standards in ICU
Rodriguez-Ruiz *et al*[113], 2022	LS online survey	HCW in ICU: 1065 in first time and 1115 in second time	Spanish ICUs in October to December 2019 and September to November 2020	MD (MMD-HP-SPA)	During the pandemic, nurses reported higher MD levels compared to the prepandemic period. ICU physicians reported significantly higher MD levels than ICU nurses during the prepandemic period, but not during the pandemic period	In Spain, during the COVID-19 pandemic, there is an increase of MD among ICU HCPs
Vlake *et al* [114], 2022	LS survey	89 post COVID patients: Male 63 (70%) and female 26 (39%)	VR efficacy data from Dutch post-ICU patients, June 2020 to February 2021; participants followed-up for 6 consecutive months	Psychological distress (IES-R) and QoL related to anxiety and depression (HADS)	High psychological distress levels in all groups. ICU-VR group showed improved ICU satisfaction with respect to the control group. 81% of patients reported a higher ICU quality, which was linked to virtual reality	ICU-VR is an innovative strategy to enhance satisfaction with ICU and improves ICU ratings aftercare, adding to its perceived quality
Fumis *et al* [115], 2022	C-S survey	Of 62 ICU physicians, 51 participated: Male 60.8%, female 39.2%; 76% married	Burnout investigated in ICU physicians during the second COVID-19 wave in São Paulo, Brazil, from December 10 to December 23, 2020	Questionnaire with demographic and occupational variables, and information on the impact of the COVID-19 pandemic on daily life (insomnia, lack of appetite, irritability, decreased libido, fear of being infected, fear of infecting loved ones, overspending) and MBI	19 (37.2%) showed high burnout, *i.e.*, 96.1% low PA, 51.0% high DP, and 51.0% high EE. Conflicts between the ICU physicians and other physicians were 50%	ICU staff have high burnout level
Levi and Moss [116], 2022	C-S survey	10 ICU nurses: 9 females and 1 male; 3 married and 7 single	ICU nurses completed psychological stress survey during the COVID-19 pandemic in southeastern United States from August to September 2020	Psychological Stress and PTSD Symptoms (PTSD Checklist), job satisfaction (a Likert-type scale), demographic information	The survey revealed 6 recurring themes: Change in Practice, Emotion, Patient's Family, Isolation, Job Satisfaction, and Public Reaction. 7 of 10 ICU nurses reported PTSD symptoms; 6 of 10 wanted to quit their jobs	Critical care nurses during the COVID-19 pandemic are highly subjected to PTSD; its early identification may prevent other related health deteriorating problems
Righi *et al*[117], 2022	C-S survey	465 long COVID patients: 54% male and 46% female; 51 % hospitalised	Patients > 18 yr with SARS-CoV-2 infection at Verona University Hospital during February 29 to May 2 2020, followed for 9 mo	Duration and predictors of symptom persistence (symptom questionnaire), physical health and psychological distress (K10)	37% of patients had at least 4 symptoms; 42% had symptom lasting more than 28 d. 19% showed psychological distress after 9 mo. Female and symptom persistence at day 28 were risk factors for psychological distress	Patients with advanced age, ICU stay, and multiple symptoms were more likely to suffer from long-term symptoms, with negative impact on both physical and mental wellbeing

Gilmartin *et al* [118], 2022	C-S survey	22 post COVID-19 patients: Male 15 (68%), female 7 (32%)	A prospective cohort study through establishing a PICS follow-up clinic at Tallaght University Hospital in October 2020 for patients who had been admitted to their ICU	PICS investigated by psychological assessment for ICU (IPAT), PTSD (PCL-5), cognitive impairment (MoCA)	IPAT score was 6.6 ± 4.6 with a PCL-5 score of 21.1 ± 17.5 and a MoCA score of 24 ± 8.4, suggestive of mild cognitive impairment	Patients have a high burden of physical and psychologic impairment 6 mo following ICU discharge for post-COVID-19 pneumonia
Guttormson *et al*[119], 2022	C-S online survey	485 ICU nurses: Female 430 (88.1%), male 56 (11.5%)	Participants recruited from national United States sample of ICU nurses, through AACCN newsletters and social media during the COVID-19 pandemic, October 2020 to January 2021	Measure of MD (MMD-HP), burnout (PROQOL-5), PTSD symptoms (TSQ), anxiety, and depression (PHQ-ADS)	Nurses reported moderate-high levels of MD and burnout; 44.6% reported depression symptoms and 31.1% had anxiety symptoms, while 47% of participants showed risk for PTSD	United States ICU nurses had high levels of anxiety and depression and higher risk for PTSD
Likhvantsev *et al*[120], 2022	C-S survey	Of 403 eligible COVID-19 patients in Russian ICUs (Moscow), 135 participated	Prospective cohort study investigated patients admitted in COVID-19 ICUs, March to June 2020	QoL (SF-36 questionnaire)	Heparin treatment in the ICU proved to be the only modifiable factor associated with an increase in the physical component of QoL	Heparin treatment enhanced QoL during COVID-19 patient recoveries at ICUs
Shirasaki *et al* [121], 2022	C-S survey	54 family members (68.5% female, 31.5% male) of 85 patients (16.7% female, 83.3% male) with COVID-19 admitted to ICU participated	PICS-F was investigated between March 23, 2020, and September 30, 2021, in Japan	PICS-F related to Psychological distress (IES-R), anxiety, and depression (HADS), and PTSD (FS-ICU)	Family members had 24% of anxiety, 26% depression and 4% PTSD	One-third of family members of COVID-19 patients admitted to the ICU had symptoms of PICS-F
Amiri Gooshki *et al*[122], 2022	C-S survey	152 patients with COVID-19: Male 55 (36.2%), female 97 (63.8%); 98 (64.47%) married	Psychological consequences of COVID-19 were investigated at hospitals in south-eastern Iran in 2020	Demographic and background information, Depression, Anxiety (DASS-21), psychological distress (IES-R)	73% of patients showed severe PTSD, 26.3% moderate depression and 26.3% severe anxiety	Higher psychological load is enhanced by ICU admission, divorce, illiteracy, and retirement
Omar *et al* [123], 2022	C-S survey	445 HCWs (physicians, nurses, and respiratory therapists): 171 ECMO-ICU, 274 non ECMO-ICU; male 239 (53.7%), female 206 (46.3%)	HCWs grouped by ECMO service (ECMO-ICU *vs* non-ECMO-ICU) and burnout status (burnout *vs* no burnout), in 8 tertiary-care hospital ICUs in Qatar, January 1 to June 30, 2021	General and demographic questions, burnout (MBI-HSS)	288 HCWs reported burnout and 158 did not. PA lower among ECMO-ICU personnel compared with those in a non-ECMO-ICU (42.7% *vs* 52.6%, P = 0.043)	High burnout in both ECMO-ICU and non-ECMO-ICU personnel
Arshadi Bostanabad *et al* [124], 2022	C-S online survey	207 ICU nurses: Male 60 (29%), female 147 (71%); 51.7% married	Psychological empowerment was investigated in Iran, from February 2021 through April 2021	Psychological empowerment questionnaire, demographic information	Positive relationship between clinical competencies and psychological empowerment (r = 0.55, P < 0.001) and between clinical competencies and work experiences (r = 0.17, P = 0.01)	Clinical competency is linked to nurse health and quality of care
Zhang *et al*[9], 2022	C-S online survey	Of 3055 eligible PICUs HCWs, 2109 HCWs completed the survey: Female 1793 (85.2%) and male 316 (14.98%); 35.04% doctors and 64.96% nurses; 1456 (69.04%) married	Online survey was administered to HCWs in the paediatric ICUs of 62 hospitals in China on March 26, 2020	General information, PTSD (IES-R), anxiety and depression (DASS-21)	970 HCWs (45.99%) reported PTSD symptoms; 39.69% had severe depression, 36.46% anxiety and 17.12% high level of stress. Married HCWs showed higher risk of PTSD than unmarried. PTSD was influenced by marital status, intermediate professional titles and exposure history; while professional titles and going to work during the epidemic were a	During public health emergencies, HCWs need specialised support

					risk factor for depression	
Kılıç and Taşgıt [125], 2023	C-S survey	93 parents who were not allowed to see their NICU babies as a response to the COVID-19 pandemic: 52 mothers (55.91%) and 41 fathers (44.09%)	Data collected between March and October 2021, in the NICU of a public hospital in Ankara, Turkey	Descriptive questionnaire, anxiety, depression, and stress (DASS-42), and Coping Style (CSS)	Depression subscale was 13.69 ± 8.86, Anxiety subscale 12.11 ± 8.37, and stress subscale 19.09 ± 9.24. CSS "self-confident" scale was 2.71 ± 0.65, "optimistic" 2.57 ± 0.59, "helpless" 2.29 ± 0.62, "submissive coping" 2.25 ± 0.49, and "seeking of social support" 2.38 ± 0.52. Participants who received information about their babies' condition by nurses had lower mean CSS "helpless" and "submissive" subscale scores than others	For parents of NICU patients need use psychological empowerment programs to help them adopt active coping strategies to deal with challenges in times of crisis
Pappa *et al* [126], 2022	C-S online survey	464 self-selected HCWs: 68% female, 32% male; nurses (43%), married (49%)	Online questionnaire sent to ICU HCWs in Greece, from May 2020, to June 2020	Depression (PHQ-9), anxiety (GAD-7) and traumatic stress (IES-R) related to burnout (MBI) and level of fear (NFRS)	Depression was 30%, anxiety 0 25% and traumatic stress 33%. Burnout was high: 65% of HCWs scored moderate-severe on EE, 92% severe on DP and 1% low-moderate on PA	Need for interventions to enhance resilience and support wellbeing in pandemic
Vranas *et al* [127], 2022	C-S survey	Of 36 eligible intensivists, 33 participated: Female 12 (36%), male 21 (64%)	Semi-structured interviews conducted on ICUs of six United states between August and November 2020	Four S (space, staff, stuff, and system) semi-structured interview, related to MD, Burnout and Fear of Becoming Infected	Restricted visitor policies and their perceived negative impacts on patients, families, and staff enhanced MD. Burnout symptoms in intensivists were enhanced by experiences with patient death, exhaustion, and perceived lack of support from colleagues and hospitals	COVID-19 pandemic reduced ICU workers' well-being, increased burnout and MD
Voruz *et al* [128], 2022	C-S survey	102 COVID-19 patients: 26 anosognosic, and 76 nosognosic patients	Tests administered by clinical psychologists and questionnaires online to patients at HUG	Neuropsychological battery (TMT, Stroop task, verbal fluency and GREFEX, backward digit span43 and backward Corsi test, Test for Attentional Performance, Rey-Osterrieth Complex Figure test, BECLA battery, WAIS-IV, QPC, BRIEF-A), psychiatric (ERQ, BDI-II, STAI, API, PTSD Checklist, GMI, DES, PSS, ESS) olfactory (Sniffing Sticks test battery), dyspnoea (self-report questionnaire), and QoL (SF-36)	Patients with anosognosia for memory dysfunction scored significantly lower on objective cognitive and olfactory measures compared with nosognosic patients; but reported significantly more positive subjective assessments of their QoL, psychiatric status, and fatigue. The number of patients exhibiting a lack of consciousness of olfactory deficits was significantly higher in the anosognosic group. Significantly more patients with lack of consciousness of olfactory deficits were in the anosognosic group, as confirmed by connectivity analyses	Cognitive disorders like anosognosia are related to different COVID-19 symptoms
Green *et al* [129], 2023	LS survey	24 ICU HCWs: 67% female, 33% male; 79% nurses	At Cedars-Sinai Medical Center (CSMC) in Los	Administered tests were: SAQ, TC, resilience (BRS),	Positive feedback paradigm enhanced resiliency and improve	Need to improve TC and resiliency. A messaging interface

			Angeles, CA, United States, over a 6-wk period from June 2020 to July 2020	burnout (BSI)	attitudes toward a TC	to exchange mutual positivity can be a simple, low-cost intervention to provide an effective peer-to-peer support system
Wozniak *et al* [130], 2022	C-S survey	3461 HCWs. 352 ICU HCWs: Female 23 (66.5%), male 118 (33.5); 242 (68.7%) married. 3109 no-ICU HCWs: Female 2327 (74.9%), male 779 (25.1%); 1973 (63.5%) married	Mental health outcomes and lifestyles change in ICU HCWs and non-ICU HCWs; the study was carried out at HUG and 8 public hospitals in Switzerland, between May to July 2020	Anxiety (GAD-7), depression (PHQ-9), distress (PDI) and Well-Being (WHO-5)	ICU HCW: 41% showed low well-being, 46% symptoms of anxiety, 46% depression and 22% peritraumatic distress. ICU HCWs scored higher than non-ICU HCWs on all tests ($P < 0.01$). Working in ICU rather than in other departments, being a woman, the fear of catching and transmitting COVID-19, anxiety of working with COVID-19 patients, work overload, eating and sleeping disorders can enhance worse mental health outcomes	High prevalence of anxiety, depression, peritraumatic distress and low well-being during the first COVID-19 wave among HCWs, especially ICU HCWs
Tariku *et al* [131], 2022	C-S survey	402 of 423 eligible participants, responded to survey: Male 233 (58.0%), female 169 (42.0%); 137 (34.1%) married	HCWs mental disease was investigate in Ethiopia, during the coronavirus disease 2019	Survey assessing the presence of common mental disorders (SRQ-20)	22.6% of mental disorders in HCWs. Being female, married, having had direct contact with COVID-19 patients, working in COVID-19 treatment centres and ICU, having any symptoms of COVID-19, and poor social support were a risk factor for mental disorders in HCWs	On-fourth to one-fifth of Ethiopian HCWs have a mental disorder during COVID-19 pandemic
Wang *et al* [132], 2021	C-S telephone survey	Of 267 eligible patients, 199 COVID-19 patients participated in the survey; male 93 (46.7%), and female 106 (53.3%); age 42.72 ± 17.53; 163 ± 81.9 married	PTSD symptoms in COVID-19 survivors investigated with telephone survey 6 mo after hospital discharge in 5 hospitals of 5 Chinese cities, August to September 2020	Somatic symptoms after discharge (PHQ-15), PTSD (PTSD-8)	7% of participants having PTSD; socio-demographic status, hospitalization experiences, post-hospitalization experiences, and psychological status enhanced PTSD symptom	Effects of COVID-19 on survivors can also involve psychological aspects and last for many months after recovery
Moll *et al*[133], 2022	LS survey	Pre-pandemic survey, 1233 HCWs, of which 572 responded (46.5%): Female 408 (71.3%), male 127 (24.9%). Pandemic survey: Of 1422 clinicians, 710 (49.9%) responded to survey; female 529 (74.5%), male 146 (20.5%)	Burnout data collected March to May 2017 and June to December 2020, during the pandemic at Emory University, Atlanta (Georgia)	Burnout (MBI)	46.5% (572 respondents) in 2017 and 49.9% (710 respondents) in 2020 shown higher burnout symptoms. Nurses' burnout prevalence increased with pandemic from 59% to 69% ($P < 0.001$), with increased EE and DP, and decreased PA. Other HCWs showed no differences in burnout levels between 2017 and 2020	Nurses are more at risk for burnout after the beginning of the COVID-19 pandemic
Groenveld *et al* [134], 2022	LS survey	Of 48 post-COVID-19 patients, 40 completed the survey: Female 68%, male 32%; median age 54 yr	Feasibility of virtual reality exercises at home for post-COVID-19 condition was investigated, between July 2020 and February 2021, in the southeast of the Netherlands	VR platform to reduce stress and anxiety and promote cognitive functioning	70% of participant report an advertising event during VR, but only 25% recall these events. 75% reports VR as having a positive influence on their recovery	VR physical exercises at home is feasible and safe with good acceptance
Lovell *et al*	LS online	240 nursing staff, 8	A before-and-after	PERMA-Profiler,	Well-being scores after	Study findings may

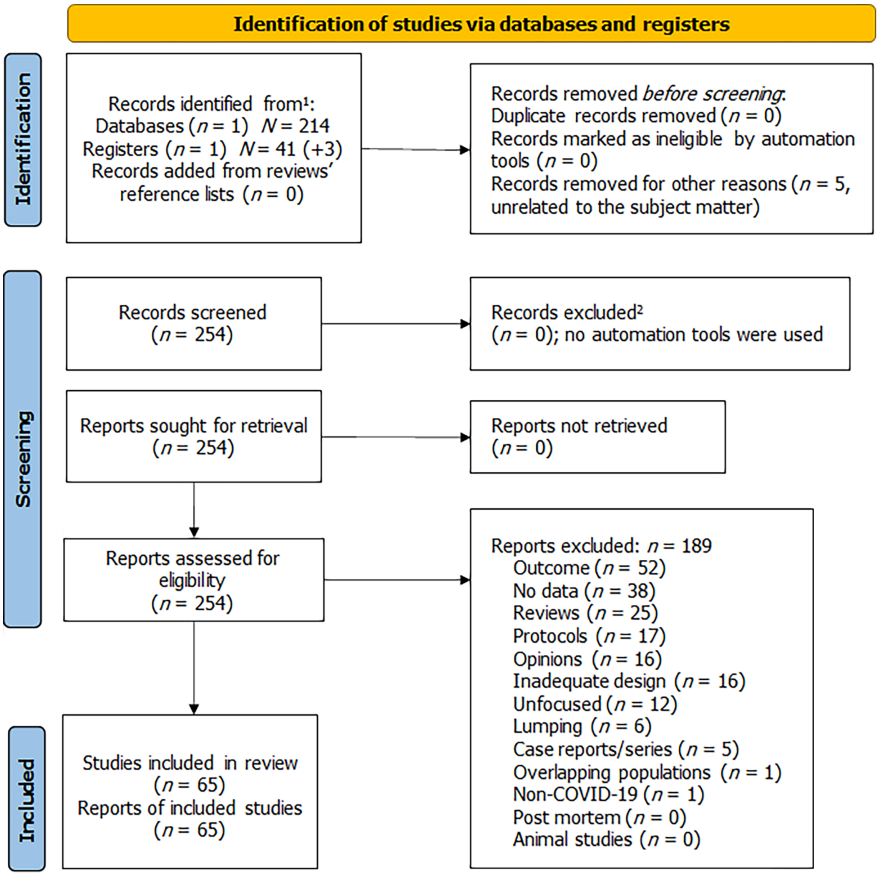
[135], 2023	Survey	permanent ICU consultants, 32 rotational registrars, 10 allied health staff members, and a team of 10 administrative and 20 operational support staff members of ICUs	interventional online study was conducted over a 2-yr period, between 2019 and 2021, in a 30-bed level-3 ICU within an Australian metropolitan teaching hospital	questionnaire to assess overall well-being (1 item), negative emotions (3 items: Sadness, anger, and anxiety), loneliness (1 item), and physical health (3 items)	the intervention were not statistically different from BL. There are three key categories: Boosting morale and fostering togetherness, supporting staff, and barriers to well-being	inform strategies for improving ICU staff members' well-being
Sun *et al*[136], 2022	C-S online survey	524 ICU nurses provided 340 valid questionnaires (64.89% actual rate); 313 females, 27 males; 229 (67.35%) married	Online questionnaire sent to ICU nurses of 15 Chinese provinces, December 2020 to January 2021	Tested calling (BCS) and resilience (BRCS) as related to thriving at work (TWS) and ethical leadership (ELS)	All variables strongly and positively correlated with each other. The high resilience group was closely associated with calling after adjusting for age, gender, marital status, and other factors	Nurses' resilience underlies their promptness to stick to their duty and calling
Chommeloux *et al*[137], 2023	LS survey	Of 80 eligible patients, 62 patients supported by ECMO for severe ARDS were included in the study	Psychological disorders of ICU patients assessed at 6 and 12 mo after ECMO onset, March to June 2020 in 7 French ICUs	Anxiety, depression, PTSD, and QoL	Mental health is one of the most impaired domains: 44% of patients had significant anxiety, 42% had symptoms of depression and another 42% were at risk of PTSD, one year after admission to an ICU	Despite partial physical recovery one year after COVID-19, psychological function remains impaired

Calling, commitment to one's duties due to internal or external value system prompts (must serve society and others, because of a supreme entity recommends so or because of one's own beliefs). AACCN: American Association of Critical Care Nurses; AMC: Academisch Medisch Centrum; API: Apathy Motivation Index; ARDS: Acute respiratory distress syndrome; BCS: Brief Calling scale; BECLA: Batterie d'évaluation Cognitive du Language; BDI-II: Beck Depression Inventory Inventory-Second Edition; BL: Baseline; BRCS: Brief Resilient Coping Scale; BRIEF-A: Behaviour rating inventory of executive function; Brief COPE: Brief Coping Orientation to Problems Experienced; BRS: Brief Resilience Scale; BSI: Burnout Scale inventory; CBCL: Child Behaviour Checklist; CBI: Copenhagen Burnout Inventory; CD-RISC2: Two-item Connor-Davidson resilience index; CI: Confidence interval; C-S: Cross-sectional; CSS: Coping Stress Scale; DASS-21: Depression, Anxiety, and Stress Scale; DES: Dissociative Experience Scale; DP: Depersonalisation scale of the Maslach Burnout Inventory; ECMO: ExtraCorporeal Membrane Oxygenation; EDMCQ: Ethical Decision-Making Climate Questionnaire; EE: Emotional exhaustion of the Maslach Burnout Inventory; ELS: Ethical leadership scale; EPDS: Edinburgh Postnatal Depression Scale; EQ-5D-3L: Euro quality of life; ERQ: Emotion Regulation Questionnaire; ESS: Epworth Sleepiness Scale; FS-ICU: Family satisfaction with the intensive care unit survey; GAD-7: General Anxiety Disorder-7 Item; GMI: Goldberg Mania Inventory; GREFEX: Groupe de Réflexion sur l'Évaluation des Fonctions Exécutives battery; GSES: General Self-Efficacy Scale; HADS: Hospital Anxiety and Depression Scale; HCAHPS: Hospital Consumer Assessment of Healthcare Providers e Systems; HCP(s): Healthcare professional(s); HCW(s): Healthcare worker(s); HPCD: Healthcare providers; HUG: Geneva University Hospitals; ICU: Inventory of Callous-Unemotional Traits; ICU(s): Intensive care unit(s); ICU-VR: Intensive care unit - virtual reality; IES-R: Impact of Event Scale-Revised; IPAT: Intensive Care Psychological Assessment Tool; ISI: Insomnia Severity Index; K10: Kessler Psychological Distress Scale; LS: Longitudinal survey; MBI: Maslach Burnout Inventory; MBI-HSS: Maslach Burnout Inventory Human Services Survey for Medical Personnel; MD: Moral distress; MMD-HP: Measure of Moral Distress for Healthcare Professionals; -SP: Spanish version; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; MPAS: Maternal Postnatal Attachment Scale; NICU: Neonatal intensive care unit; NFRS: Numerical fear rating scale; PA: Personal accomplishment of the Maslach Burnout Inventory; PCL-5: Post-Traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders-5th Edition; PCQ: Psychological Capital Questionnaire; PICS: Post-intensive care syndrome; PICS-F: Post-intensive care syndrome-Family; PICU: Paediatric intensive care units; PDI: Peritraumatic Distress Inventory; PHQ-9: Patient Health Questionnaire-9; PHQ-ADS: Patient Health Questionnaire Anxiety and Depression Scale; PM: Pearlin Mastery Scale; PROQOL-5: Professional Quality of Life Scale; PsyCap: Positive psychological state, psychological capital; PSS-10: Perceived Stress Scale-10; PSS:NICU: Parental Stressor Scale:Neonatal intensive care unit; PTSD: Post-traumatic stress disorder; PTSS: Post-traumatic stress symptoms; QPC: Cognitive Complaints Questionnaire; QoL: Quality of life; Q3PC: Cognitive Screening, European AIDS Clinical Society cognitive screening questions; RESE: Regulatory, Emotional Self Efficacy Scale; RS-14: 14-item Resilience Scale; RSA: Resilience Scale for Adults; SAQ: Safety Attitude Questionnaire; SAS: Self-rating Anxiety Scale; SCL-90: Symptom Checklist 90; SDS: Self-rating Depression Scale; SFSW: Finnish Strongest Families Smart Website; SF-36 Questionnaire: Short Form Health Survey-36 item questionnaire; SRQ-20: Self-Reporting Questionnaire; SRSS: Self-rating sleeping situation scaling; TC: Teamwork climate; TMT: Trial making test; TSQ: Trauma Screening Questionnaire; TWS: Thriving at work scale; VAS: Visual Analogue Scale; VR: Virtual reality; WHO-5: World Health Organization Well-Being Index; WAIS: Wechsler Adult Intelligence Scale-Fourth Edition; WSAS: Work and Social Adjustment Scale.

infection[32]. However, ICU patients with COVID-19 on clozapine did not differ for outcome from those receiving other antipsychotics[33].

Psychological implications of being hospitalised in an ICU: ICU post-discharge

As previously mentioned, the ICU exposes patients to stressful experiences with potential long-term repercussions. People who overcome a critical phase of illness and ICU admission can develop a post-intensive care syndrome (PICS), a cluster of physical, cognitive, and mental impairments observed after ICU hospitalisation; this shares clinical features with depression, anxiety, and PTSD[34]. The main risk factors for developing PICS can be classified as interventional, environmental, and psychological factors, including treatments such as mechanical ventilation, unfamiliar environment, and severe stress



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Figure 1 Results of our database searches for psychological consequences of the coronavirus disease 2019 pandemic on intensive care units and possible psychological interventions according to the recommendations of the Preferred Reporting Items for Systematic Reviews statement. [1]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). [2]If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. COVID-19: Coronavirus disease 2019.

experienced during hospitalisation[26,35].

The emergence of the COVID-19 pandemic has increased the number of patients exposed to risk factors of PICS and who require intensive care and aftercare[20]. Furthermore, a COVID-19 patient in the ICU who develops acute respiratory failure, is likely to be exposed to increased use of sedation and limited physical therapy in addition to mechanical ventilation. Therefore, critically ill COVID-19 patients have high chances of developing PICS[23]. Patients with COVID-19 who were treated in the ICU and survived have higher risk due to visit restriction, prolonged mechanical ventilation, higher sedative exposure, and reduced availability of physical therapy[36], but they are also at risk of developing prolonged cognitive dysfunction[37]. Generally, after ICU hospitalisation, mental health problems are very common and often impact health-related quality of life. These include anxiety, depression, and PTSD, as well as guilt, reduced libido, social isolation, irritability, and low confidence [38].

During the pandemic, PTSD appears to have a high incidence, of about 30%[39], characterised by symptoms such as hypervigilance, avoidant behaviour, and re-living the traumatic experience. In particular, hypervigilance may result in panic responses, irritability, and altered sleep-wake cycle, or in overconfident behaviour or, as in the case of COVID-19 patients, with concern about contagion and re-exposure[23]. Sometimes patients may present with disturbing and intrusive memories related to hospitalisation. Specific stimuli, such as smells, images, and sounds, may also activate memories. In addition, some patients may be inclined to avoid any medical environment after ICU admission[23].

COVID-19 and its complications, long hospital stay, and side effects of medications lead to reduced physical capacity that can affect mood. Recent literature has shown that both patients with COVID-19 and those without have high rates of post-hospitalisation depression[40], as well as anxiety and insomnia[41]. However, ICU patients with COVID-19 and ICU patients without COVID-19 did not differ on psychological distress, *i.e.*, cumulative symptoms of PTSD, anxiety, and depression three months after discharge, thus suggesting not to focus exclusively on COVID-19-positive patients[42].

During the COVID-19 pandemic, another major problem was social stigma[43]. In some cases, patients experienced guilt or shame for passing the disease on to others, with ensuing difficulty in

returning to their customary daily lives[23]. Multidisciplinary critical care, in addition to preventing imminent death, lays the foundation for improving patients' overall long-term survival experience[44].

Interventions aiming at addressing the psychological implications of COVID-19: Interventions with patients

In general, in patients admitted to the ICU, it is important to consider not only physical health but also mental health. This was especially important in COVID-19 patients, as high mortality and unpredictability had peculiar psychological meanings and consequences[45]. Attention is also due to patients with a previous history of mental disorder, as social isolation and estrangement can make the individual particularly vulnerable to psychopathological breakdown events. For this reason, during the pandemic, healthcare personnel has worked closely with psychologists to monitor the psychological condition of patients[45]. In this study, an in-person psychological intervention aimed at preventing unpleasant outcomes was encouraged in the most severe cases, which can result in aggression, self-injurious behaviour, and suicide attempts. Psychological support, taking care to use individual precautions aiming at reducing the risk of infection, was based on the assessment of the patient's prior state of mental health (traumas, previous episodes of self-harm, *etc.*) and his/her social and family environment. It is also important to take into account the potential impact of COVID-19 on the patient's socio-economic status[45].

In some ICUs, interventions such as music therapy or meditation were performed to mitigate the anxiety and distress of patients[46]. The addition of available technological devices such as TV, laptop, or radio may alleviate the patient's sense of isolation[46]. Sometimes psychological support for COVID-19 patients in ICU has been conducted remotely, through the use of digital tools. In particular, phones and the internet have proven to be effective in treating psychological issues[45]. Technology has also allowed ICU patients to keep in touch with their relatives, with tablets and mobiles provided for this purpose[46]. As mentioned above, patients may experience psychological sequelae even after discharge from the ICU. Early psychological interventions can support the patient in regaining ordinary daily routine. To treat PTSD, anxiety, worry, and panic reactions the use of cognitive behavioural therapy or metacognitive therapy could be given a trial, as these techniques have shown some efficacy in all these conditions[47,48]. In this framework, psychoeducational interventions are used to teach the patient to manage possible stress reactions[49]. Online support groups led by a psychologist can help COVID-19 survivors to share emotions related to the period experienced in the ICU[23].

Interventions aiming at addressing the psychological implications of COVID-19: Interventions with family members

Family members of patients admitted to the ICU are at high risk of developing psychological disorders. Anxiety, depression, PTSD, and other trauma-related reactions are the most common. In the literature, this clinical condition is called PICS-family[26,50]. During the COVID-19 pandemic, these symptoms can exacerbate due to the isolation family members suffer and the impossibility to get into direct contact with their loved ones. In addition, family members are often positive for COVID-19 and isolated at home, and this generates a sense of helplessness and loneliness in patients[45,51]. Relatives play a fundamental role, especially when the patient is dying because they have to make decisions for him, or to defend his/her interests[50].

For these reasons, it is important to design interventions that help preventing psychological dysfunctions among family members and support them in decision making during this difficult moment. In this frame, the psychologist is responsible for establishing clear criteria, that are shared with all health care professionals, to determine whether and how to intervene[52]. The psychological needs of family members to consider in the development of these interventions are the following: The need to be informed and updated about the medical condition of their loved one, the need to be emotionally supported by receiving reassurance and listening, the need to maintain a connection with the patient, even at a distance, and the need to receive support during the grieving process in case of death of their loved one[53]. In all these situations, it is important not to view as pathological any emotional reactions of family members but to consider them as being normal in the context of the difficult moment they are experiencing[52].

Most interventions aimed at family members used digital tools to reduce the possibility of transmitting COVID-19. Phone and video calls were the preferred tools for addressing relatives' psychological needs[54,55]. However, in case of a high psychopathological risk, family members were allowed to access the ICU. For instance, in-person visits accompanied by the psychologist were encouraged to preserve the relationship between the patient and his/her relatives. Personal protective equipment was used to protect all those involved[53].

Interventions aiming at addressing the psychological implications of COVID-19: Interventions with health workers

During the pandemic, intensive care workers, exposed to a high workload and high risk of infection, reported states of severe anxiety, insomnia, irritability, anxiety, and fear[56]. For this reason, ICU

healthcare professionals also seemed to be at serious risk of developing a burnout syndrome. The main factors associated with this risk include weak communication among staff members as well as organisational difficulties[57].

This highlighted the need to develop interventions aimed at ensuring ICU health care professionals' well-being and preventing emotional distress. These interventions must be designed on the basis of certain primary needs, *i.e.*, the need to feel safe, the need to belong to a unit group with clear, well-defined, and shared goals, the need to be listened to and, finally, the need to emotionally decompress [53]. The literature has confirmed the need for psychologists and psychological interventions in ICUs even during the pandemic; in fact, the applicability of psychological knowledge and skills to staff well-being before and during the pandemic were shown for example to promote teamwork and group cohesion and also to lead defusing activities[53]. Indeed, group defusing can allow for reframing the meaning of a traumatic event by reducing its emotional impact[58]. Defusing is the process of helping a disaster victim through the use of brief conversation and may help survivors in shifting from a survival mode to focusing on practical steps to reach stability again and to better understand the thoughts and feelings linked to their experience of the disaster[59]. Defusing involves professionals in three stages with different functions. Introduction is the general presentation of the intervention to clarify and engage participants. Exploration is the moment in which traumatic experiences related to working in ICU emerge or are extracted, through the recollection of particular thoughts and emotions. Information aims to normalise stress reactions by providing continuous support, reassurance, and coping strategies to address emotional distress[60]. As the pandemic is still persisting or returning under new forms, rapid, pandemic-specific assessment tools may be needed to allow better evaluation of patients' stress in the ICU[61].

It may also be useful to set up a room for the ICU healthcare professionals to allow them to offload tensions by promoting physical and psychological decompression[53]. Relaxation techniques showed efficacy in managing stress, preventing burnout, and increasing work motivation, in particular autogenic training[62]. Relaxation techniques during COVID-19 confirmed their effectiveness as procedures apt to improve quality of life, work motivation, burnout and stress perceptions within the emergency department team[63].

Psychological interventions in this field should be considered as preventive and proactive health interventions, rather than as treatments for psychopathological problems, helping individuals to effectively express their own resources. Emergency psychology has offered appropriate techniques to achieve this goal[64]. Summarising, COVID-19 pandemic has highlighted the importance of frontline workers' mental health and the need to support the presence of psychologists in ICUs; in this way, healthcare workers could experience more relief from the many responsibilities that hamper the effectiveness of their work[45].

Humanised technology during COVID-19 pandemic: Digital communication

During COVID-19 pandemic in ICUs, patients' possibilities to see their relatives were reduced[65]. In this context, digital communication proved to be a very effective tool for facilitating communication despite visitation restrictions[66]. Digital interactions can bring significant benefits in terms of emotional support and communication of information to family members, and also in terms of patient recovery and increased ICU staff moral[22].

Recent studies have mainly explored the impact of digital interventions on family members: COVID-19 pandemic has reduced the possibility to see the patient and directly interfacing with the medical teams to receive clinical updates. In general, allowing family members to use video calls to see their loved ones has proven to be a good way to alleviate the discomfort of physical distance[54]. Other studies show that family members report mixed feelings about video calls with the patient. For example, they wanted the opportunity to see the patient but reported that the images of their loved ones lying down were upsetting. This fact underlines the importance of assessing each individual family for burden and preferences[67].

Regarding communication between family members and the medical team, phone calls were used as a tool to communicate quick information[54]. Video calls, instead, were preferred to align doctors and family members' perspectives on the patient's condition. Doctors' doubts about their capacity to transmit empathy at a distance were denied by family members' opinions, who reported a sense of closeness when using a telephone or a video, despite the distance[66]. An Italian team developed ten statements and two checklists to enable medical teams to communicate effectively with family members, that could be also used as guidelines[68].

It is appropriate at this point to talk about the barriers limiting the use of digital tools in intensive care. In fact, family members do not always have the necessary skills to access the set video platforms or they not even possess a suitable technological device. Problems with the Wi-Fi connection and, in some cases, lack of time and of specific training in the staff add to the above-mentioned barriers[22].

Humanised technology during COVID-19 pandemic: VR interventions

Several ICUs during the COVID-19 pandemic used VR interventions to deal with patients' psychological symptoms such as anxiety, stress, PTSD, and depression[69]. VR bring the user into a "realistic, immersive multi-sensory environment" through computer-generated visuals[70] and this digital tool

proved to be effective in reducing anxiety and pain, by distracting the user and providing a relaxing experience[71]. In the presence of full-blown PTSD, VR can subsequently be used as 'exposure therapy'; it can promote deep involvement and activation of the user's traumatic memory of fearful stimuli[72], such as those experienced in an ICU[73]. For this reason, VR exposure therapy turned out to be also one of the most popular game-based digital interventions for the treatment of depression caused by fear [74], although in PTSD patients, it did not reduce the anxiety and did not differentiate from other standard treatments[75].

The use of VR as a therapy for the psychological sequelae of COVID-19 patients has some important advantages. First, it could be helpful for reconstructing the phases the patient experienced during the ICU hospitalisation, so to adjust to unpleasant memories, as proposed in a protocol[76]. Second, it can be used remotely to respect social distance needs. Third, it allows to manage more patients at the same time. However, VR implementation should overcome some barriers. These mainly concern the organization of VR interventions at home and remote support. For this purpose, it is necessary to design a toolkit that is safe, comfortable, and easily accessible[70].

Other possible applications of VR during COVID-19 pandemic in ICU include its use to rapidly upskill healthcare professionals and to reduce perceived interindividual stress[56], but also to improve communication of information about ICU treatment and ICU environment to patients' relatives (ICU-VR-F)[77].

Current and future perspectives

The present review identified 65 studies targeting COVID-19 in ICUs and the ensuing psychological problems, of which 43 focused on the role of the psychologist in increasing team cohesion, reducing distress of patients, relatives, and staff and preventing or reducing burnout in the latter, and highlighting that during the COVID-19 pandemic the psychologist is playing an increasingly important role within the ICU.

Special psychological needs emerged for the patient and his/her relatives, and also for healthcare professionals. Frequently psychologists acted promptly through interventions aimed at providing psychological support to all involved and facilitating communicative exchanges, despite the restrictions imposed. In this way, the medical team members were relieved of much workload and were free to focus mainly on the medical aspects of the cases inside the ICU[74].

As the coordinated interventions of the medical team and the psychologist has proven to be very effective in patient care and in promoting patient well-being, it is desirable that the presence of the psychologist becomes a structural feature of ICUs and other hospital areas that deal with emergencies. Based on the literature, digital tools were much used in ICUs during the COVID-19 pandemic to promote communication between patients, family members, and healthcare professionals[56,77]. The addition of new learning-based approaches, such as deep learning or machine learning[78] may help people overcoming this difficult moment by implementing psychological techniques[79]. Since the risk of contagion is still high, they can still be used - when in-person visitation is not strictly necessary - to make communication easier.

VR is a particular technological tool, which is useful in treating psychological sequelae of ICU inpatients. It is mostly used during the COVID-19 pandemic and can significantly improve the mental health of previously hospitalized patients. For their numerous benefits, digital tools, including VR, should be commonly used in ICUs. For this to be possible, however, it is necessary to overcome the previously outlined limitations and barriers.

Limitations

We did not include in our review other databases that could have accrued our results. The obtain results used diverse methodologies, leading to heterogeneity which did not allow us to perform sound statistical analyses such as meta-analyses or meta-regressions. We did not include specific distinctions regarding the target audience (geriatric patients, neonatal ICUs, or patients with disabilities), so we collected all studies independently from methodology. As a result, we cannot make generalizations regarding the efficacy or effectiveness of the mentioned interventions. Some of these interventions could be modified or adapted according to patients' needs.

CONCLUSION

In this review, we analysed the role of the psychologist in the ICU during the COVID-19 pandemic, focusing on the interventions with patients, family members, and healthcare professionals. We chose a narrative review of the literature because currently there is dearth of studies focusing on the psychologist's work in ICUs during the public health emergency represented by COVID-19. This fact, and the fact that the methodologies of the studies we were able to gather are heterogeneous, make the field not meta-analysable. Since the COVID-19 pandemic is not still over, we need further studies to support the standpoint that psychological support in the ICU is fundamental.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) upset intensive care unit (ICU) function, increasing risk for psychological distress during and after hospitalisation. This paved the way for psychological interventions to support patients in ICUs.

Research motivation

To alleviate the increased workload and burden of ICU staff through psychological interventions.

Research objectives

We carried out a systematic review of the psychological issues raised in ICUs during the COVID-19 pandemic which concerned patients, their relatives, and the ICU staff (physicians, nurses, and auxiliary staff) as well as of the possible psychological treatments that could improve psychological measures.

Research methods

Search of PubMed and ClinicalTrials.gov databases, establishing inclusion/exclusion criteria and deciding eligibility through Delphi rounds among involved researchers.

Research results

We found 65 eligible articles, which summarised. Results point to increased perceived stress and psychological distress in staff, patients and their relatives. Some psychological interventions hold promise.

Research conclusions

Psychological programmes to improve psychological measures in ICU patients, relatives, and staff may enhance ICU functional efficiency.

Research perspectives

The role of interventions using digital tools and virtual reality may pave the way to a better work climate within ICUs, with psychologists gaining a liaison role within the staff.

FOOTNOTES

Author contributions: Monti L and Marconi E contributed equally to this work and share first authorship. Monti L, Marconi E, and Bocci MG conceived the review; Kotzalidis GD, Mazza M, Galliani C, and Tranquilli S made literature searches and shaped the review; Vento G and Conti G implemented the database; Monti L, Marconi E, Bocci MG, Kotzalidis GD, Mazza M, Galliani C, and Tranquilli S provided the first draft; Sani G, Antonelli M, and Chieffo DPR supervised the writing of the manuscript; Monti L, Tranquilli S, and Kotzalidis GD provided the final draft; and all authors read and approved the final draft and revision.

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EDITORIAL

Catatonia: "Fluctuat nec mergitur"

Gabor S Ungvari, Stanley N Caroff, Levente Csihi, Gábor Gazdag

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Abstract

In the beginning of the 1900s, the prevalence of catatonia in inpatient samples was reported to be between 19.5% and 50%. From the mid-1900s, most clinicians thought that catatonia was disappearing. Advances in medical sciences, particularly in the field of neurology, may have reduced the incidence of neurological diseases that present with catatonic features or mitigated their severity. More active pharmacological and psychosocial treatment methods may have either eliminated or moderated catatonic phenomena. Moreover, the relatively narrow descriptive features in modern classifications compared with classical texts and ascribing catatonic signs and symptoms to antipsychotic-induced motor symptoms may have contributed to an apparent decline in the incidence of catatonia. The application of catatonia rating scales introduced in the 1990s revealed significantly more symptoms than routine clinical interviews, and within a few years, the notion of the disappearance of catatonia gave way to its unexpected resurgence. Several systematic investigations have found that, on average, 10% of acute psychotic patients present with catatonic features. In this editorial, the changes in the incidence of catatonia and the possible underlying causes are reviewed.

Key Words: Catatonia; Historical overview; Frequency of catatonia; Diagnostic and Statistical Manual of Mental Disorders-5; Wernicke–Kleist-Leonhard school; Bush-Francis Catatonia Rating Scale

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Core Tip: Although the prevalence of catatonia was reported to be between 19.5% and 50% in the early 1900s, most clinicians thought that catatonia was disappearing by mid-century, However, more recent systematic investigations have found that catatonia continues to be a common clinical disorder with an average prevalence of 10%. The apparent historical changes in the prevalence of catatonia reflects shifts in the socio-cultural context of psychiatry, the type of service, diagnostic criteria, research methods, and advances in treatment and clinical practice. We propose the establishment of an international society and journal dedicated to the study of catatonia to facilitate understanding and research.

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INTRODUCTION

During most of the last century, in line with the prevailing Kraepelinian tradition, catatonia essentially was used to refer to catatonic schizophrenia, although a careful reading of Kraepelin's textbook shows a more sophisticated view of catatonia[1-4]. In the two authoritative classical textbooks, the prevalence of catatonia in inpatient samples is reported to be between 19.5%[1] and 50%[5], whereas it was 35.4% according to the Wernicke–Kleist–Leonhard school[6]. However, from the mid-1900s, there was a growing consensus among clinicians that catatonia was becoming nearly extinct, as Mahendra[7] famously asked, "Where have all the catatonics gone?". Such clinical impressions were supported by a few, although not all[8,9], epidemiological studies that attempted the nearly impossible task of determining the changes in the real prevalence of catatonia across several years or decades against the background of shifts in the socio-cultural context of psychiatry, the type of service (inpatient, outpatient, and community), diagnostic criteria, research methods, and advances in treatment and clinical practice in general.

DISCUSSION

Relatively comparable, albeit not necessarily reliable, rough estimates of the changes in the frequency of catatonia can be made by focusing on single sites when comparing two time periods. For example, between 1850 and 1950, the rate of first admissions for catatonia decreased from 6% to 0.5% in the Bethlem royal hospital, a leading hospital and academic center in London, United Kingdom[10]. Another example from Finland showed a decline in the frequency of admissions for catatonic schizophrenia from 40.1% to 11% over just 20 years from 1933–1935 to 1953-1955[11]. In two Polish hospitals, where catatonia was diagnosed very conservatively, the frequency of catatonic schizophrenia diagnoses decreased 190-fold from 1924–1929 to 1994–1999 and 36-fold from 1958–1963 to 1994–1999[12]. From 1964 to 1984, catatonic schizophrenia nearly disappeared entirely in a university hospital in Santiago, Chile[13]. In a Belgian academic center, based on a chart review of 19309 admissions, the diagnosis of catatonic schizophrenia decreased from 7.8% to 1.3% in the two consecutive decades of 1980–1989 and 1990–2000[14].

Several plausible reasons have been proposed for the decline in the rate of catatonia observed in the second part of the last century. Advances in medical sciences, particularly in the field of neurology, may have reduced the incidence of neurological diseases that present with catatonic features or mitigated their severity[7]. More active pharmacological and psychosocial treatment methods may have either eliminated or moderated catatonic phenomena. Moreover, the relatively narrow descriptive features in modern classifications compared with classical texts and ascribing catatonic signs and symptoms to antipsychotic-induced motor symptoms may have contributed to the reduced incidence of catatonia[15, 16]. The application of catatonia rating scales introduced in the 1990s[17] revealed significantly more symptoms than routine clinical interview, suggesting that insufficient diagnostic practices were responsible for the under-recognition of catatonia[14].

From the 1990s, the situation changed, and within a few years, the notion of the disappearance of catatonia gave way to its unexpected resurgence[18,19] (Figure 1). Several systematic investigations have found that, on average, 10% of acute psychotic patients present with catatonic features[20], with a wide range of frequencies from 1% in Nigeria[21], 3.7% in Mexico[22] to 38% in Greece[23], 50% in Belgium[24] and 68% in the United States[25]. The corresponding figures reached 20% for depression [26], 31% for mania[27], and almost 100% for the chronically hospitalized psychotic population[28]. Awareness has also broadened to encompass catatonia occurring in the context of general medical conditions[16,18]. Since the 1990s, interest in the epidemiological[16], clinical[29,30] and neurobiological [31,32] aspects of catatonia has continued unabated, stimulated by its semi-independent place in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition[33,34] and in addition to secondary catatonia occurring in the context a wide range of psychiatric and medical conditions also appeared as an independent diagnostic category in the International Classification of Diseases, 11th revision[35].

The apparent disappearance of catatonia from psychiatric practice and research for decades and its recent re-discovery raises serious questions. The intriguing fact is that a well-known and easily observable motor phenomena, which has been reported in such a high proportion in acute psychiatric admissions over the past two decades, was declared to be essentially extinct for approximately four decades in the second part of the last century. The logical argument is that, if catatonia had temporarily become extinct, there must have been a very significant environmental and/or neurobiological change responsible for this, which went unnoticed for a while and then stopped. However, there has been no suggestion that such panoramic environmental or biological changes affecting motor symptoms in psychiatric patients have occurred. However, if catatonia did not actually disappear, which is the likely scenario, the question remains how mainstream psychiatry missed an important aspect of mental disorders for decades. A possible answer to this puzzling question may provide important information about the nature of catatonia and psychiatric diagnostic practice. However, this is a complex issue and reaching a firm conclusion is unlikely as the available studies on catatonia are fraught with major methodological flaws that make it difficult to make comparisons between studies across time[16].

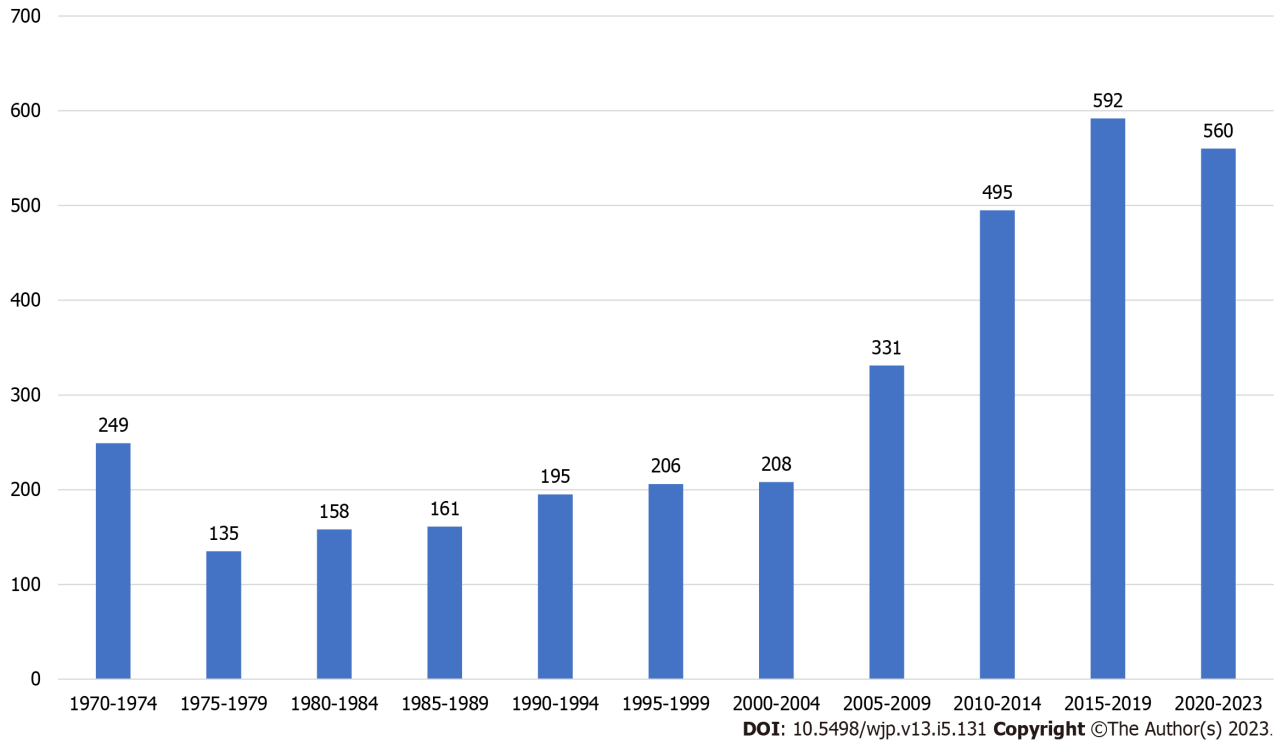
We posit that catatonia may have been modified in its manifestations and may have lessened in intensity and frequency due to advances in treatment of schizophrenia and mood disorders, but never disappeared entirely[15]. Rather, it was not given adequate attention by clinicians, particularly in the internationally dominant Anglo-American psychiatry with pockets of exceptions in Europe, such as at the Wernicke–Kleist-Leonhard school of psychiatry[6,36]. There are also indications that catatonia never disappeared in developing countries[37], but has occurred at a similar or even higher frequency and severity to those in Western settings[38] albeit possibly with a different symptom profile[39]. Over the past three decades, several Indian studies examined the phenomenology[40,41] and the frequency of catatonia in acute inpatient admissions that ranged from 4.8%[40] to 10.3%[41], 16.3%[42] and 37.2%[43].

In the following section, we outline some of the factors that support our view that the disappearance of catatonia was apparent, but not real. From a broader perspective, the temporary disappearance of catatonia in psychiatric research and practice during the middle decades of the 20th century is the logical consequence of the development of psychiatry in the last century.

In the second part of the 20th century, the whole fabric of psychiatric practice moved away from traditional stand-alone institutions that existed at the fringes of society to a more community and office-based model focused on outpatient therapy. From the 1920s, psychodynamic psychiatry, based on psychoanalysis and its versions, had an increasingly large impact on mainstream psychiatry, mainly in the United States and to a lesser degree in other Western countries, although isolated examples of biologically-oriented descriptive psychiatry, such as the Wernicke–Kleist–Leonhard school or French neuropsychiatry[44] never ceased to exist in continental Europe. As psychodynamic psychiatry focuses on the inner psychic life of the patients and not the observation of patients' manifest behavior or motor symptoms, catatonia lost its significance in English-language psychiatry, and its signs and symptoms were glossed over in diagnostic practice.

Diagnostic practices have also undergone profound changes from the 1960s with the introduction of objective rating scales[45] and then operationalized diagnostic criteria in the 1970s[46]. The original psychopathological descriptions, including those for catatonia, were made by psychiatrists who had the opportunity to observe their patients every day in different situations over several weeks, months, or years. Many of these psychiatrists actually lived in the institutions and had fewer commitments outside of their clinical work than their modern counterparts. The democratization and decentralization of psychiatric practice, coupled with the widespread introduction of simplified cross-sectional diagnosis, as in the Diagnostic and Statistical Manual of Mental Disorders third edition[47], greatly altered the relationship between patients and psychiatrists and the diagnostic process.

In the developed world, this situation emerged starting in the 1960s with the arrival of de-institutionalization; the establishment of short-term acute psychiatric wards in general hospitals; community outpatient psychiatry evolving to brief 15-min "med checks"; and the collaborative role of allied mental health professionals providing psychiatric services, just to mention a few important factors. As a result, psychiatrists began spending less and less time in direct contact with their patients in the modern era, which may have reduced the likelihood of detecting catatonic symptoms. For instance, restructuring a regional psychiatric service in the United Kingdom resulted in psychiatrists having access to "less than 20% of the total case-load"[48].



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Figure 1 Published articles on catatonia based on PubMed broken down by 5 years.

Another aspect of contemporary psychiatric practice that may have hindered the easy detection of catatonia is exemplified by a landmark study conducted at the Institute of Psychiatry in London, one of the leading academic psychiatric centers in the world that have provided the scientific foundation to sanction diagnostic practices in the modern era[49]. In a series of diagnostic exercises, 28 psychiatrists with at least 4 years of clinical experience were asked to diagnose patients during the same 5-min diagnostic interviews based on either a video of the patients during the interview, a soundtrack recording of the interview, or only written transcripts. Surprisingly, the diagnostic accuracy measured against the final hospital discharge diagnoses was essentially identical in these three different diagnostic situations. Kendell came to the important conclusion that observing the patients' behavior did not improve diagnostic accuracy, indicating that behavioral or motor symptoms had no, or negligible, currency in the diagnostic process although this academic center stressed the importance of behavioral symptoms and careful observations. Kendell also found that diagnostic accuracy did not increase after 4 years spent in psychiatric practice, thereby questioning the value of accumulated experience and the power of observation developed during this experience in making a diagnosis. Furthermore, based on the diagnostic accuracy of 70% reached after 5 min in each rating situation, the author suggested significantly shortening the standard 1-hour diagnostic interview. The implications of these findings on the under-recognition of catatonia are obvious.

It is well known from classical textbooks that the frequency and intensity of catatonic episodes fluctuate over time[1,5,6] and that they may not manifest at the time of cross-sectional assessment, which is how modern catatonia rating scales are conducted, resulting in a potential failure to detect the whole scope of catatonic symptomatology, particularly in chronically ill patients. For example, the Bush–Francis Catatonia Rating Scale (BFCRS)[17], the most widely used rating instrument, requires only 5–10 min to complete, although raters are encouraged to consult their medical notes covering the previous 24-h period, albeit only for the items of "withdrawal" and "autonomic abnormality." The BFCRS has been shown to be adequate for assessing acute catatonic episodes[17], but it may not be entirely sufficient for persistent or periodic catatonia in patients with chronic illness[50], as previously suggested[51]. A study comparing the number and severity of catatonic signs and symptoms covered by the BFCRS, rated by skilled clinicians, with the "gold standard" of extended, unobtrusive observations by an experienced clinician found that the latter method yielded significantly higher ratings[52]. Signs and symptoms that were most frequently missed by cross-sectional assessment, but captured by longitudinal clinical observations were mannerisms, stereotypy, grimacing, perseveration, and apparently purposeless impulsivity[52].

Following the widespread introduction of antipsychotic drugs in psychiatric practice in the mid-1950s, it took about a decade to recognize the full spectrum and significance of drug-induced motor symptoms and syndromes referred to as extrapyramidal side effects (EPS). The importance of EPS in psychiatry may have overshadowed catatonic and other illness-related motor symptoms in clinical practice. Catatonic signs and symptoms may have been obscured by and ascribed to drug-induced EPS

[15]. EPS-like motor symptoms have been consistently reported in drug-naïve patients since the 1990s, raising the possibility that, in many instances, catatonia may have been indeed misdiagnosed as EPS [53]. Even if this were not the case, the recognition of motor symptoms in drug-naïve patients helped refocus attention to catatonia.

CONCLUSION

We believe that the growing number of publications on catatonia and the number of clinicians and researchers displaying a keen interest in this subject have reached the level that warrants the establishment of an international society and a journal dedicated to the study of catatonia, to bring together interested parties, promote and coordinate research, and disseminate relevant knowledge to the broader mental health community. This may be one the avenues to further facilitate a greater understanding of catatonia, thereby improving the lives of patients with catatonia.

FOOTNOTES

Author contributions: Gazdag G and Ungvari GS outlined the content of the editorial; Ungvari GS prepared the first draft of the manuscript, Caroff SN, Csihi L and Gazdag G critically reviewed and corrected the manuscript; All authors approved the final version of the text.

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OPINION REVIEW

Differences between DSM-5-TR and ICD-11 revisions of attention deficit/hyperactivity disorder: A commentary on implications and opportunities

Rapson Gomez, Wai Chen, Stephen Houghton

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Abstract

Current ICD-11 descriptions for attention deficit hyperactivity disorder (ADHD) were recently published online, in the same year as the DSM-5-TR (text revised edition) was released. In this commentary, we compare and contrast the DSM-5/DSM-5-TR and ICD-11 diagnostic criteria, summarize important differences, and underscore their clinical and research implications. Overall, three major differences emerge: (1) The number of diagnostic criteria for inattention (IA), hyperactivity (HY) and impulsivity (IM) symptoms (*i.e.*, DSM-5-TR has nine IA and nine HY/IM symptoms, whereas ICD-11 has eleven IA and eleven HY/IM symptoms); (2) the clarity and standardization of diagnostic thresholds (*i.e.*, the diagnostic thresholds for symptom count in IA and HY/IM domains are explicitly specified in DSM-5-TR, whereas in ICD-11 they are not); and (3) the partitioning of HY and IM symptoms into sub-dimensions (*i.e.*, difference in partitioning HY and IM symptom domains relates to the differences between the current and previous editions of DSM and ICD, and this has important research implications). Currently, no ICD-11 based ADHD rating scales exist and while this absence represents an obstacle for respective research and clinical practice, it also presents opportunities for research development. This article highlights these challenges, possible remedies and novel research opportunities.

Key Words: Attention deficit hyperactivity disorder; ICD-11; DSM-5-TR; Clinical implication; Diagnostic threshold; Taxonomy; Research

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Core Tip: Three major differences between DSM-5-TR and ICD-11 are: (1) The number of diagnostic criteria for inattention, hyperactivity (HY) and impulsivity (IM) symptoms; (2) the clarity and standardization of diagnostic thresholds; and (3) the partitioning of HY and IM symptoms into sub-dimensions between previous and current editions of DSM and ICD. Currently, no ICD-11 based attention deficit hyperactivity disorder (ADHD) rating scales exist. The absence of research evidence to inform and reconcile these differences represents opportunities for research. Emerging research findings suggest that 'impulsivity' is likely the key latent factor underlying different expressions of ADHD symptoms; and the current criteria merging HY/IM could limit such explorations.

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INTRODUCTION

ICD-11 descriptions for attention deficit hyperactivity disorder (ADHD) were recently published online [1]. In addition, the DSM-5-TR[2] was published in print along with a more extended digital e-edition version. While there is greater alignment between ICD-11 and DSM-5-TR, there are nevertheless differences (albeit subtle in parts), which entail important implications for research and clinical application. This commentary paper critically distils and articulates these differences (particularly diagnostic symptoms and symptom threshold for diagnosis). As no revisions were made to the diagnostic criteria of ADHD in DSM-5-TR, the remainder of this commentary refers to DSM-5-TR instead of 'DSM-5' or 'DSM-5 and DSM-5-TR', unless otherwise specified. A more severe variant of ADHD is called hyperkinetic disorder (HKD) in ICD-10[3]. The symptom compositions for HKD in ICD-10 are comparable with the 'combined presentation' of ADHD in DSM-5-TR, but not the 'predominantly inattentive' or 'predominantly hyperactive-impulsive' presentations. The ICD-11 revision of ADHD is now more aligned with DSM-5-TR, by including less severe presentations/types other than HKD.

With reference to DSM and ICD comparisons, we first summarize the major differences between DSM-5/DSM-5-TR and ICD-11 diagnostic criteria. The implications of these differences for clinical practice and research are then discussed. To place our discussion in context, we present first a summary of DSM-5-TR and ICD-11 and compare them. By undertaking this commentary we seek to facilitate a deeper understanding and appreciation of these different, but related, classification systems, and how they contribute to better research and clinical practice.

Summary of DSM-5-TR and ICD-11

Table 1 provides a summary of DSM-5-TR and ICD-11 diagnostic criteria for ADHD in relation to their descriptions, onset, presentation patterns, and symptom criteria, with regards to settings, duration and impairment. As can be seen in Table 1, while there is much alignment between ICD-11 and DSM-5-TR, important differences exist, especially in terms of symptom composition and criteria. We will focus on these in the next section.

MAJOR DIFFERENCES BETWEEN DSM-5-TR AND ICD-11

There are at least four major differences between DSM-5-TR and ICD-11 and their previous editions that are noteworthy of consideration.

Difference in splitting one inattentive symptom criterion

First, in contrast to DSM-5-TR which lists nine inattention (IA) symptoms, ICD-11 has 11 IA symptoms. The specific DSM-5-TR IA symptom for "Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities" is split into two separate IA symptoms in ICD-11: "Lacking attention to detail", and "Making careless mistakes in school or work assignments". This gives rise to the first extra symptom.

Additional IA and hyperactivity/IMP symptoms in ICD-11

In addition, the specific DSM-5-TR IA symptom "Is often forgetful in daily activities" is also partitioned into two separate similar IA symptoms in ICD-11: "Is forgetful in daily activities" and "Has difficulty remembering to complete upcoming daily tasks or activities". This gives rise to the second extra

Table 1 Comparison of DSM-5-TR and ICD-11 diagnostic criteria for attention-deficit/hyperactivity disorder

	DSM-5-TR	ICD-11
Name	ADHD	ADHD
Onset	Some symptoms present before 12 yr	Some symptoms present before 12 yr
Symptoms	9 IA symptoms	11 or 9 IA symptoms
	9 HY/IM symptoms	11 or 10 HY/IM symptoms
Presentation types/symptom criteria for children	(1) ADHD combined: At least 6 IA and 6 HY/IM symptoms; (2) ADHD predominantly inattentive: At least 6 IA symptoms; and (3) ADHD predominantly hyperactive/impulsive: At least 6 HY/IM symptoms	(1) ADHD combined: IA and HY/IM symptoms present with neither predominating; (2) ADHD predominantly inattentive: IA symptoms predominating; and (3) ADHD predominantly hyperactive/impulsive: HY/IM symptoms predominating
Presentation types/symptom criteria for persons aged ≥ 17	(1) ADHD combined: At least 5 IA and 5 HY/IM symptoms; (2) ADHD predominantly inattentive: at least 5 IA symptoms; and (3) ADHD predominantly hyperactive/impulsive: At least 5 HY/IM symptoms	
Settings	Present in at least 2 settings	Multiple settings–but symptoms may vary according to the structure and demands of the setting
Duration	≥ 6 mo	≥ 6 mo
Impairment	Social, academic, or occupational functioning	Social, academic, or occupational functioning–IA symptoms less evident in stimulating and rewarding activities and HY/IM during free-play

ADHD: Attention deficit hyperactivity disorder; IA: Inattention; HY: Hyperactivity; IM: Impulsivity.

symptom. A new IA symptom for ICD-11, not present in DSM-5-TR, is "Frequently appears to be daydreaming or to have mind elsewhere". This is the third extra symptom. However, this symptom could be regarded as being more in line with the "sluggish cognitive tempo (SCT)" symptom when considered in light of the SCT literature[4]. In addition, the specific DSM-5-TR IA symptom "Often has trouble holding attention on tasks or play activities" is not present in ICD-11.

With reference to hyperactivity (HY)/impulsivity (IM) symptoms, ICD-11 lists 10. Two of these relate to overactive behavior: "Has difficulty sitting still without fidgeting" and "Feelings of physical restlessness, a sense of discomfort with being quiet or sitting still". ICD-11 specifies that the former be applied to younger children, and the latter be applied to adolescents and adults (*i.e.*, age 17 years or older). These can be regarded as developmental variants of the same symptom. For this reason, there are in reality 10 HY/IM symptoms in ICD-11. The symptom of "is often 'on the go', acting as if 'driven by a motor….' experienced by others as being restless…" in DSM-5-TR is absent in ICD-11; however, this could potentially be comparable to 'feelings of physical restlessness' in ICD-11. A new HY/IM symptom in ICD-11, which is absent in DSM-5-TR, is "A tendency to act in response to immediate stimuli without deliberation or consideration of risks and consequences (*e.g.*, engaging in behaviors with potential for physical injury; impulsive decisions; reckless driving)". This symptom captures the classical description of dispositional trait IM. In contrast, in DSM-5-TR, IM is solely represented by three directly observable behavioral symptoms (*i.e.*, 'blurt out', 'can't wait' and 'interrupt'), as an absence of deliberation or risk consideration that cannot be directly observed, but often only inferred or disclosed by the actor upon retrospective reflection.

In summary, DSM-5-TR has nine IA and nine HY/IM symptoms, whereas ICD-11 has 11 IA and 11 HY/IM symptoms (but 10 if 'fidgeting' in children and 'mental restlessness' in adults are combined as one).

Differences in partitioning of HY and IM symptom sub-dimensions

The third difference relates to previous and current editions of DSM and ICD. Specifically, whether HY and IM symptoms should be considered as separate dimensions by contrasting DSM-IV-TR[5] with DSM-5-TR, and by contrasting ICD-10 with ICD-11. Currently, in DSM-5-TR, HY and IM symptoms are considered to represent a single dimension regarding threshold for diagnosis. This means an adult will meet diagnostic threshold of the HY/IM domain regardless of whether they have HY or IM symptoms. The HY/IM threshold can be met by two different adults: One with five HY symptoms and another with mixed two HY symptoms and 3 IM symptoms. Although ICD-11 also groups HY and IM as a single dimension, diagnostic thresholds are not specified for either children or adults.

In the previous DSM-IV-TR edition, symptoms were listed separately under HY and IM subheadings. Likewise, ICD-10 contemporaneous with DSM-IV-TR also considered them separately, but with 'talkativeness' listed within the IM grouping. By applying the ICD-10 framework, it can be postulated that out of the 10 ICD-11 HY/IM symptoms, five symptoms are HY ('motor activity', 'leaving seat', 'running

about', 'difficulty setting still'/'physical restlessness', and 'difficulty in not engaging in activity quietly'), while the other five symptoms ('talkativeness', 'blurt out', 'can't wait', 'interrupt', and 'immediate response without considering consequences') are IM symptoms. Recent empirical findings from factor analytic studies provide support that HY and IM symptoms should be grouped separately, and that 'talkativeness' should be grouped with IM rather than HY in line with ICD-10 configuration[6,7].

Differences in clarity and standardization of diagnostic thresholds

Fourth, the diagnostic thresholds for symptom count in IA and HY/IM domains are explicitly specified in DSM-5-TR (*i.e.*, six for each domain for children and five for each domain for adolescents/adults aged 17 or above), whereas in ICD-11 they are not.

Noting that ADHD symptoms may vary with developmental age and ADHD severity, ICD-11 states that "several symptoms" from the IA and HY/IM clusters need to be present. This approach is however consistent with the general approach used by ICD-11[8], in order to avoid arbitrary cutoffs related to symptom counts and duration; and as such, terms such as "several days", "several weeks", and "several symptoms" are used in ICD-11.

The approach used by ICD-11 is considered to be more in line with how clinicians actually make diagnoses, allowing more flexibility in exercising clinical judgment and avoiding algorithmic requirements (regarded by some as 'pseudo-precision'), such as a prescribed threshold of symptom counts. This flexibility is an innovative feature in ICD-11, and is more consistent with the dimensional classification[8]. However guidelines on how to establish thresholds are not provided in ICD-11. Therefore, when using ICD-11, the onus is placed on individual clinicians to apply their own judgement in determining clinical thresholds. The potential problems with this approach include diagnostic difficulty (especially for less experienced clinicians) and the increased heterogeneity of ADHD above and beyond that yielded by the DSM-5-TR defined ADHD diagnostic criteria.

IMPLICATIONS OF THE DIFFERENCES BETWEEN DSM-5/DSM-5-TR AND ICD-11 FOR RESEARCH AND CLINICAL PRACTICE

With reference to ADHD diagnostic criteria, the differences related to the number of criteria, the thresholds for ADHD diagnosis, and whether the HY and IM symptom groups are merged or grouped separately have a number of implications for clinical practice and research.

First, in relation to clinical practice, as mentioned previously, the thresholds for the different symptom domains are unspecified in ICD-11, thereby increasing the likelihood of greater diagnostic heterogeneity. Greater standardization generally improves diagnostic reliability, but this prescribed algorithmic approach is not adopted by ICD-11 per se; in contrast, ICD-11 prefers the dimensional approach. In this respect, we suggest that until clearer guidance from ICD-11 and its future revision is forthcoming, researchers using ICD-11 should be cognizant of providing very detailed descriptions of the samples (including symptom count) examined in their studies. Moreover, it is anticipated that ICD-11 will in due course release its Clinical Descriptions and Diagnostic Guidelines (CDDG). These will likely provide more operationalized diagnostic guidance for clinicians and researchers, and with more than a decade of work invested in their development[8], be 'designed to assist mental health clinicians in making a confident diagnosis'. We therefore highly recommend readers to access and study in detail the ICD-11 CDDG for more information, when it becomes available.

Secondly, for DSM-5/DSM-5-TR, questions have been raised about whether the proposed/implied two-factors (*i.e.*, IA and HY/IM dimensions) is the optimum structural model. This is because many studies that have compared different latent structural models of ADHD have reported less support for the two-factor model than for three-factor models (especially IA, HY and IM factors aligned to ICD-10 [3]. Relatedly, recent studies[7,9] have provided empirical support for the S-1 bifactor model to account for the latent factor structure of ADHD. That is, ADHD is likely a disorder predominantly driven by latent IM substrates[7] in line with the 'trait impulsivity hypothesis'[10]. In this S-1 bifactor model, 'impulsivity' is best represented by four ICD-10 IM items ('talkativeness', 'blurt out', 'can't wait' and 'interrupts') in line with the ICD-10 configuration, rather than the DSM-5-TR three IM items ('blurt out', 'can't wait' and 'interrupts'). A consistent finding in these studies is that the HY factor is poorly defined (insignificant and/or negative loadings) and lacks reliability (omega coefficient levels below 0.50). Therefore HY is observable in individuals with ADHD, the relevance of HY for ADHD at the latent trait levels is questionable.

These considerations have important research implications that can potentially be compromised by the current ICD-11 and DSM-5-TR definitions. At present we lack knowledge about the psychometric properties of ICD-11 ADHD symptoms, and therefore need to use caution when using ICD-11 for clinical practice relating to ADHD. Indeed, for this reason, some in clinical practice may question the present clinical utility of ICD-11, until greater clarity emerges.

Thirdly, the differences indicate that existing measures, such as DSM-5 based ADHD ratings scales, may not be appropriate for ICD-11 defined ADHD assessment, and that there is a need to develop new ADHD rating scales based on ICD-11. The absence of ICD-11 based rating scales for ADHD can be

considered an important obstacle for research and clinical practice using ICD-11. However, as a temporary solution, researchers could utilize the listed criteria as defined by ICD-11. Notwithstanding this, the absence of a validated ICD-11 defined rating scale, or a measurement instrument or semi-structured diagnostic tool to capture the full range of ICD-11 symptom criteria, provides opportunities for researchers to construct appropriate measures with empirically derived reliability and validity. This is important as the identification of the underlying structure will be determined not only by the clinical elements, but also by the scope of the tools that are used in its recognition. The absence of thresholds for the IA and HY/IM symptom groups in ICD-11 means that for clinicians who still wish to use ICD-11 for clinical diagnosis of ADHD, the onus is placed upon them to use their own cut-off scores to establish clinical caseness. This approach is likely to reduce inter-rater and test-retest reliability, thereby increasing the heterogeneity of ADHD beyond what we currently observe when DSM-5 ADHD diagnostic criteria are applied. Additionally, such a scenario would limit the comparability of findings across studies in which the diagnostic caseness is based on ICD-11. It is also conceivable that the failures of DSM-5-TR and ICD-11 in classifying and partitioning HY/IM symptoms into respective HY and IM subdimensions will dissuade researchers from further exploring the three-factor structure of ADHD (*i.e.* IA, HY and IM three subdimensions), or the S-1 bifactor modelling in which different patterns of partitioning HY and IM symptoms are evaluated[7].

Another issue relevant to research and clinical practice here is biomarkers. The World Federation of Societies of Biological Psychiatry and the World Federation of ADHD previously concluded that there is still no reliable biomarker for ADHD[11]. Nevertheless potential promising candidates should be further explored[12,13]. When the roles of different biological markers become established, they may play a role in improving diagnostic precision and reducing heterogeneity, and may contribute towards differentiating the validity and utility of DSM-5-TR and ICD-11 with respect to their differences as identified in this review.

CONCLUSION

In this commentary, we have articulated the differences in diagnostic criteria of ADHD between DSM-5-TR and ICD-11 and the implications of these differences for clinical practice and research. The major differences were noted in symptom composition and diagnostic thresholds for the IA and HY/IM domains. The clinical and research implications of these include: (1) The current lack of rating scales and measurement tools to capture the full spectrum of ICD-11 symptom items; and (2) the lack of standardized diagnostic threshold for the IA and HY/IM symptom domains in ICD-11, with ensuing problems for validity, reliability and increased heterogeneity. Moreover, the lack of distinction between HY and IM symptoms run contrary to recent empirical findings and limit future opportunities to explore the three-factor or S-1 bifactor modelling of IA, IM and HY as key components in the latent structure of ADHD. In closing, this commentary seeks to provide clinicians and researchers with a succinct summary of the issues, as well as important insights, regarding the clinical and research implications of the recent changes in DSM-5-TR and/or ICD-11.

FOOTNOTES

Author contributions: Gomez R reviewed the literature and drafted the manuscript; Chen W conceived the idea for the manuscript, reviewed the literature and revised the manuscript; Houghton S reviewed the literature and revised the manuscript.

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REVIEW

Resilience by design: How nature, nurture, environment, and microbiome mitigate stress and allostatic load

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Abstract

Resilience to psychological stress is defined as adaption to challenging life experiences and not the absence of adverse life events. Determinants of resilience include personality traits, genetic/epigenetic modifications of genes involved in the stress response, cognitive and behavioral flexibility, secure attachment with a caregiver, social and community support systems, nutrition and exercise, and alignment of circadian rhythm to the natural light/dark cycle. Therefore, resilience is a dynamic and flexible process that continually evolves by the intersection of different domains in human's life; biological, social, and psychological. The objective of this minireview is to summarize the existing knowledge about the multitude factors and molecular alterations that result from resilience to stress response. Given the multiple contributing factors in building resilience, we set out a goal to identify which factors were most supportive of a causal role by the current literature. We focused on resilience-related molecular alterations resulting from mind-body homeostasis in connection with psychosocial and environmental factors. We conclude that there is no one causal factor that differentiates a resilient person from a vulnerable one. Instead, building resilience requires an intricate network of positive experiences and a healthy lifestyle that contribute to a balanced mind-body connection. Therefore, a holistic approach must be adopted in future research on stress response to address the multiple elements that promote resilience and prevent illnesses and psychopathology related to stress allostatic load.

Key Words: Resilience; Stress; Allostatic load; Epigenetics; Circadian rhythm; Attachment; Oxytocin; Diet; Microbiome; Exercise

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Core Tip: There are multiple reviews in the literature that address different factors contributing to resilience, an adaptation to stress. To our knowledge, none of these reviews takes into consideration the complexity of the system that leads to allostasis or allostatic load, an indicator of physiologic "wear and tear" resulting from repeated exposure to stress and inability to cope. The purpose of this review is to shed light on the complexity of the system and discuss the molecular mechanisms that may contribute to resilience. Lastly, we conclude by emphasizing the need for a comprehensive approach to reduce stress allostatic load.

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INTRODUCTION

According to the American Psychological Association (APA), "resilience is the process and outcome of successfully adapting to difficult or challenging life experiences, especially through mental, emotional, and behavioral flexibility and adjustment to external and internal demands". Adaptation to adversities depends on several factors: Individual's engagement and view of the world, the availability of social and communal resources, and the use of specific coping strategies (APA, 2022, https://www.apa.org/topics/resilience). It is worth noting that resilience and coping are inter-related but have different constructs with respect to their impact on behavioral changes[1]. While coping manages stressful events by using cognitive and behavioral strategies[2], resilience refers to the adaptive capacity to recover from traumatic or stressful situations[3].

Research in humans over the last two decades has demonstrated that resilience and use of adaptive coping skills in the face of adversity in both children and adults are the main factors that protect from developing mental and physical illnesses. While personal characteristics such as personality traits of persistence and determination, and cognitive flexibility are key elements, perceived parental care, adolescent peer relationships, adult romantic relationships, community support systems, dietary lifestyle, exercise, and circadian rhythm are all implicated in building resilience[4-11]. Resilience is an active adaptive process that helps mitigate negative social, psychological, and biological consequences of extreme stress[12]. The adaptive behavioral manifestations of resilient people are described as enhanced internal locus of control, self-efficacy, happiness, life satisfaction, the ability to derive a sense of life meaning, ability to foster social and communal interactions, and problem-solving skills[13,14].

Fostering resilience early in life may be an effective preventative measure prior to the development of trauma[15]. It is estimated that 60% of men and 50% of women would experience at least one potentially traumatic event in their lifetime, however only 8% of women and 4% in men develop post-traumatic stress disorder (PTSD) (National Center of PTSD, 2022, https://www.ptsd.va.gov/). The development of resilience is an ongoing dynamic process throughout the lifespan in both children and adults, even in those who have suffered from adverse early life experiences, to successfully adapt to or overcome traumatic stress-related illnesses[16,17]. Indeed, resilience can aid in developing positive changes in the aftermath of traumatic events, such as gaining the capacity to relate to others, personal strength, spirituality, and life appreciation[18]. Resilience is implicated in changes in brain regions involved with the social networks that promote empathy, social connectedness, and modulation of central responses to stress[19].

The objective of this review is to summarize the existing knowledge about the multitude factors and molecular alterations that result from resilience to stress response. Our aim is to create awareness for future research studies on allostatic load and stress response about the intricate network contributing to resilience. The methodology we used is Literature Review performed through PubMed, PsycINFO and Scopus databases for peer-reviewed English-language articles published prior to December 2022 using the following keywords: Chronic stress, allostatic load, trauma, biomarkers, circadian rhythm, resilience, neurobiology, genetic, epigenetic, attachment, oxytocin, gut microbiome, diet, mindfulness, exercise, and psychotherapy. We will first describe the existing knowledge about the biologic aspects of the stress response and implications of chronic stress. Then we will present the different factors that contribute to resilience and associated molecular changes.

STRESS RESPONSE AND HYPOTHALAMIC-PITUITARY-ADRENAL ACTIVATION

The neurohormonal mechanism of stress response

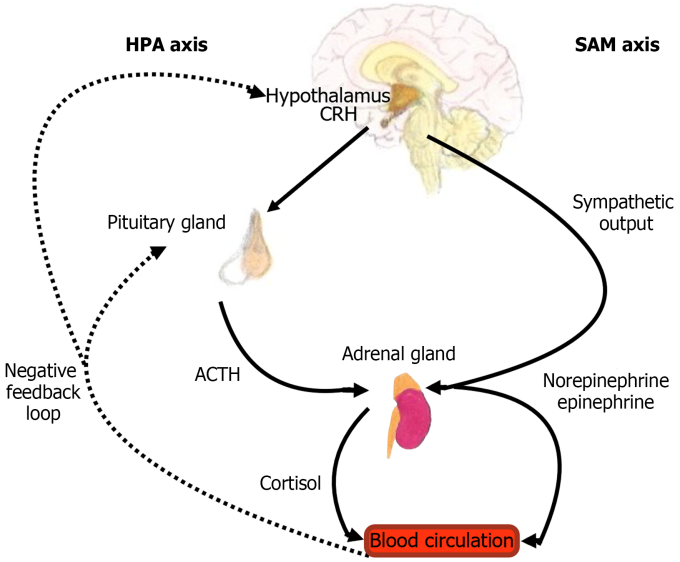
The stress response involves a neurohormonal mechanism activated by the cross talk of the hypothalamic-pituitary-adrenal (HPA)-axis and the sympathetic-adrenal-medullary (SAM)-axis that results in widespread hormonal, neurochemical, and physiological alterations. The SAM axis activates the peripheral sympathetic nervous system to release epinephrine and norepinephrine[20,21]. HPA axis activation leads to a cascade of events whereby corticotropin releasing hormone released from the hypothalamus stimulates the release of adrenocorticotropic (ACTH) from the pituitary gland, which in turn results in production of glucocorticoids (GCs) from the adrenal cortex. GCs, also known as cortisol in mammals and corticosterone in rodents, regulate cellular function by interacting with steroid receptors that modulate the neural circuitry and neuroendocrine systems involved in behavioral responses to stress[21]. These receptors, glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), are expressed throughout the brain, mostly in the prefrontal cortex (PFC), hippocampus, amygdala, and other limbic and midbrain structures[17,22]. Under conditions of threat, HPA activation leads to increased release of GCs to promote acute survival by mobilizing stored energy, hence contributing to a state of increased arousal and vigilance. The stress response is then terminated by a negative feedback loop that attenuates the HPA-axis at the level of GR, causing GCs levels to return to normal (Figure 1)[23]. In contrast to GR, MR modulates basal and stress-induced HPA-axis activity to appraise stress and fear-related memories. Enhanced expression and function of MR may improve resilience to traumatic stress and reduces the risk for psychiatric disorders[21]. Studies have shown that MR dampen glucocorticoid receptor sensitivity to stress *via* regulation of FK506-binding protein 5 (FKBP5), a potent negative regulator of glucocorticoid signaling that plays an important role in fine-tuning the MR:GR balance in the hippocampus[24].

When the HPA axis is activated, dehydroepiandrosterone (DHEA) is also released by the adrenal glands along with GCs. DHEA is an important mediator of the HPA axis since it facilitates the N-methyl-D-aspartate receptor function, antagonizes g-Aminobutyric Acid A receptors, and facilitates metabolism of cortisol to the inactive metabolite cortisone. DHEA-Sulfate (DHEA-S), a more potent form than DHEA, plays a neuroprotective role by inhibiting GC effects at the level of the GR as well as supporting neurogenesis[25-28]. Cortisol/DHEA-S ratio represents a balance between the catabolic effects of cortisol and the anabolic, regenerative function of DHEA-S[27,29]. In fact, a higher DHEA-S to cortisol ratio predicted stress resilience in male military personnel, lowering symptoms of PTSD and showing greater improvement over time[30]. On the other hand, a lower resting DHEA/cortisol ratio has been associated with childhood trauma[26].

Circadian control of the HPA axis

Multiple studies have demonstrated the close connection between the circadian rhythm and stress systems to maintain allostasis. The homeostasis of the HPA axis, which produces the primary mediators in adaptation to stress, is closely regulated by the circadian rhythm output[31]. The nearly 24-h periodic peripheral rhythms are controlled by the master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN generates a daily rhythm of transcription and translation feedback loop that align with the 24-h external light-dark environment[32]. The central clock in the SCN orchestrates peripheral clocks at the cellular level to synchronize physiological and behavioral rhythms and regulates the activity of various humoral and neuronal allostatic mediators, among which GCs that show a robust time-of-day dependence[33-35]. These robust circadian dynamics of the allostatic mediators enable the host to flexibly respond and adapt to various physiological stressors[36,37]. In this current modern society and lifestyle that humans live in, where light at night is widespread due to adoption of electrical light, we developed a deranged temporal adaptation that our physiological systems have not evolved to cope with. The chronic disruption of circadian rhythms predisposes to physiologic and behavioral changes that can lead to maladaptive allostatic mechanisms and compromising resilience[32,36].

Animal studies have shown that disruption of the circadian rhythm by misalignment to the natural light/dark cycle in mice results in neurobehavioral changes resulting in decreased complexity of neurons in the prefrontal cortex, the brain center involved in executive and emotional control, and reduction in cognitive flexibility[38]. Even short-term circadian misalignment has been shown to disrupt memory consolidation in response to fear-conditioning that could compromise resilience[39]. The bidirectional communication between the central clock and HPA axis is also evident by circadian disruption in response to early life stress that contributes to metabolic derangement occurring later in life[40]. Hence, re-alignment of circadian rhythms by following the natural light/dark cycle can enhance allostatic adaptive resilience and can be especially beneficial for individuals with psychiatric disorders who struggle with sleep disturbances[41-43]. Interestingly, timing of Trauma Exposure therapy to specific trauma-associated cues can have a different outcome in the process of healing. One study found that exposure to trauma cues is more efficacious when administered during the morning time compared to the evening[44,45].



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Figure 1 Hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, neurohormonal output, and feedback loop. CRH: Corticotropin releasing hormone; HPA: Hypothalamic-pituitary-adrenal; SAM: Sympathetic-adrenal-medullary; ACTH: Adrenocorticotropic; ACTH: Adrenocorticotropic hormone.

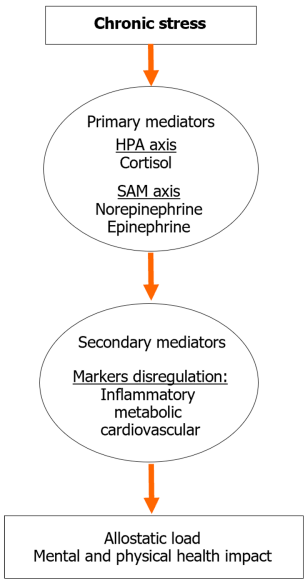
Chronic stress and allostatic load

As presented above, exposure to stress triggers several biological mechanisms in the body that release stress hormones as primary mediators in order to adapt to short term or acute stress. Maintaining stability through change is a phenomenon known as allostasis[46,47]. Allostasis is considered a beneficial adaptive mechanism that promotes host survival through the appropriate activation of energetic resources[48]. However, repeated exposure to stress, also known as chronic stress, can result in prolonged activation of the HPA and SAM axes, which may lead to activation of secondary inflammatory and metabolic mediators, and ultimately lead to deleterious effect on metabolic, immune, and cardiovascular functions as well as brain and behavior (Figure 2)[49-52]. The cumulative effects of chronic stress reduce the ability of the host to flexibly cope with subsequent stressful situations, which lead the system to shift from allostasis to allostatic load or physiological "wear and tear"[53-56].

Impact of chronic stress on brain and gene expression

While it is beyond the scope of this minireview to discuss all the structural, biological and genetic modifications in response to chronic or developmental stress, we will briefly discuss few structural changes and gene variants involved in the stress response, which may result in either negative or positive associations to resilience. Animal studies have shown structural changes in different brain regions whereby chronic stress increases dendritic spine number or branching in the amygdala and nucleus accumbens, reduces dendritic arborization and glutamatergic dendritic spine density of pyramidal neurons in PFC and hippocampus, and decreases hippocampus neurogenesis[57].

The impact of the environment and specifically early life stress profoundly alters key genes involved in stress response *via* epigenetic modification. Many of these genes can be modified through epigenetic alterations and variation in microRNAs (miRNA), short non-coding RNAs detected in body fluids, in response to environmental influences[58,59]. Little is known about the role of miRNA in psychiatric disorders and resilience. One animal study showed that the systemic knockdown of miRNA-144-3p reduced the depression-like phenotype in stress-susceptible mice[60]. Another study demonstrated that knockdown of miRNA-144 and miRNA-33 in the hippocampus increased the proportion of resilient female animals[61]. Studies also showed that low maternal care is associated with epigenetic modification by increased methylation of the gene encoding GR (*NR3C1*), leading to decreased GR expression in the hippocampus[62,63]. Another important player in regulating the stress response is the *FKBP5* gene. This gene modulates intracellular glucocorticoid signaling and homeostatic regulation of the stress response[64]. Studies have shown that epigenetic modifications induced by early life stress or single nucleotide polymorphisms (SNPs) in human *FKBP5* gene result in differential induction of the FKBP5 protein upon glucocorticoid stimulation, thereby adding to the variability of stress perception and response, and increasing the risk of developing stress-related psychiatric disorders[65,66].



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Figure 2 Impact of chronic stress on allostatic load mediated by primary and secondary biomarkers. HPA: Hypothalamic-pituitary-adrenal; SAM: Sympathetic-adrenal-medullary.

FACTORS CONTRIBUTING TO BUILDING RESILIENCE

Role of psychosocial interventions: Brain and epigenetic alterations

While early-life stress can induce permanent changes in behavioral and physiological responses to stress through epigenetic modification, DNA methylation is potentially reversible through intervention. Using blood samples from human, methylation levels of specific regions within *FKBP5* and brain derived neurotrophic factor (*BDNF*) were changed in response to psychotherapy and were associated with recovery and improvement[67,68]. For example, Exposure-based Cognitive Behavioral Therapy results in a decrease in *FKBP5* methylation and leads to a positive treatment response[69]. Furthermore, maternal stroking and tactile stimulation can normalize DNA methylation in the leukocytes of infants who had been exposed to high levels of pre- and postnatal maternal depression[70]. Mindfulness practice is well known to improve cognitive and social functioning, and reduce symptoms of depression and anxiety[71,72]. The mechanisms whereby mindfulness regulates the stress response is through activation of brain regions involved in interoception, self-awareness, emotion regulation, and threat detection[73-75]. Mindfulness practice has been shown to alter different immune and endocrine pathways, as well as epigenetic methylation of the *FKBP5* gene in adults with PTSD[76-78].

These findings are in line with animal studies demonstrating that intervention by enrichment can reverse the epigenetic, plasticity, and behavioral deficits in rats exposed to early life stress[79]. Indeed, our group has recently published a new treatment approach, Cue Centered Therapy (CCT) for complex developmental trauma in children and adolescents. CCT emphasizes resiliency and positive adaptation factors by using the life timeline as a core component for both positive and negative events in youth's life. CCT has shown effectiveness in improving functioning and reducing child and parent post-traumatic stress. Treatment outcome research of CCT have demonstrated PTSD symptom improvement as measured by cortical activation patterns using functional near-infrared spectroscopy, a non-invasive neuroimaging technique[80,81].

Role of oxytocin and attachment

Another important molecular determinant of resilience is oxytocin (OXT), which is closely tied to attachment. Humans are considered social mammals that develop various forms of social attachments and bonds from infancy throughout life[82,83]. The influence of secure attachment to a caregiver modulates physiology and behavior and is essential for a healthy psychological development and well-being. Attachment is a psychological/behavioral construct for infant's self-regulation that is promoted and facilitated by caregiver's ongoing emotional availability. Infants internalize their interactions with their caregiver and build internal working models that represent their attachment figures in relation to themselves[82]. Attachment styles during early life predict moderate stability of attachment over the years but can be susceptible to change by significant relationship experiences[84]. The different attachment styles are believed to have a profound shaping of an individual's emotional and psychosocial functioning as well as resilience or predisposition to psychopathology[85-87].

It is established that sudden separation of children from their parents, interpreted as abandonment, threatens the attachment bond and results in profound sense of shame and complex emotions especially in the absence of adequate support[88,89]. In addition to the impact of separation on secure attachment, transgenerational maternal experiences with unresolved attachment to their own caregivers can influence the quality of bonding of those mothers to their children. Children of mothers who exhibit higher distress and disruptive behavior exhibited a significantly higher cortisol compared to ones with no disruptive behavior[90]. These differences in cortisol levels and behavior may be related to gene polymorphism of the OXT and OXT receptor (OXT-R) in children from mothers with negative maternal experiences. These genes moderate the stress response of children, and polymorphisms can be associated with the disorganized behavior independent of maternal experiences[91].

The OXT system activated through social interaction is thought to have an important implication in building resilience by playing an important role in the regulation of affective and social behaviors as well as modulating stress response[92-94]. OXT is a neuropeptide produced by hypothalamic paraventricular, supraoptic, and accessory nuclei, and is released to the posterior pituitary gland and ultimately to the peripheral blood circulation[95,96]. In addition to OXT's role in parturition and lactation[97], the neuropeptide plays a key role in promotion of postnatal sensitive maternal caregiving to optimize infant's social and emotional development[98-100]. Higher levels of OXT have been linked with increased attention to social cues[101] while lower levels have been seen in maltreated children [102]. A positive association between OXT level and interpersonal bonding and affiliation, as well as stress modulation in interpersonal situations is well established. In animal models, OXT facilitates mating-induced pair bonds *via* mesolimbic dopamine system, however, variation in striatal OXT-R density predicts resilience and susceptibility to neonatal social neglect[103,104]. Growing evidence from animal and human studies showed that OXT signaling early in life by parental nurturing can buffer against physical and emotional stressors and help establish the neural networks needed during adult life to form social bonds[105-110].

Maternal care during early life, which overlaps with behaviors involving OXT in mother and infant through embedded hidden regulators, maintains the stress hyporesponsive period and direct HPA maturation during heightened plasticity[62]. It has been established that early life stress in human and non-human primates is associated with changes in cerebrospinal fluid OXT level and social behavior, as well as the ability of parental presence to attenuate stress response to a novel environment[111-113]. Animal studies have shown that OXT controls the secretion of ACTH under stress condition and enhance the long-term HPA axis response to stress in adult rats, which may act as a feedback regulator to enhance recovery from stress-related symptoms[114-116].

OXT seems to play an important role in fear modulation where it strengthens fear memory to predictable or cued fear while attenuating fear memory to unpredictable, diffuse threats (contextual fear and non-cued fear)[117-122]. Thus, OXT fosters adaptive defensive behaviors and accurate fear discrimination of relevant and imminent threats, yet reducing sustained fear responses to distant threats[123]. Animal studies have shown that administration of OXT by intracerebroventricular injection or intranasally facilitated cued fear extinction and reduced chronic stress-induced deficits in fear extinction in male rats, respectively. In contrast, administration of OXT-R antagonist impaired fear extinction in male rats[124,125]. These studies emphasized the role of OXT in reducing sustained fear responses and anxiety-like behaviors while strengthening fear responses to relevant and predictable threats. Nuclei of the central amygdala are the main output that connect to the brainstem to eventually mediate the fear response, including freezing behavior. OXT-R transmission in the amygdala switches from passive freezing to active escape behaviors in confrontation with an imminent, but escapable threat[126-128]. OXT also mediates affiliate and prosocial behaviors. OXT-R signaling facilitates social transmission of fear between familiar conspecifics, which might serve as warning system of impeding threat[129,130].

SNPs of the OXT-R gene, rs53576, has been shown to be associated with individual differences in social and emotional abilities, predisposition to psychopathology, and environmental adversity in the prediction of anxiety and depression[131-138]. Human brain-imaging studies in repeated childhood trauma and emotional neglect have demonstrated structural and functional variations in the amygdala, hypothalamus and cingulate gyrus in response to OXT-R gene polymorphism leading to variations in social and behavioral outcomes[139]. Furthermore, epigenetic alterations to specific OXT-R gene polymorphisms can attenuate resting parasympathetic tone and increasing central amygdala grey volume, thereby altering traumatic stress reactivity[140].

Role of diet, gut microbiome, and exercise

There is an extensive connection between the mind and body in which the wellbeing of one influences the other. A major element of this mind-body connection is the brain-gut axis. Indeed, there is an association between early life adversities and changes in the brain-gut axis that may occur *via* pathways related to glutamatergic excitotoxicity and oxidative stress, predisposing to negative mood and stress [141].

Maternal diet and resilience: The quality of dietary interventions during a critical period of neural development predicts the function of the brain-gut axis and plays a key role in building resilience to stress. Earlier studies showed that maternal nutrition during pregnancy plays a fundamental role in

intrauterine developmental programming and predicts child's resilience to stress and vulnerability to psychiatric disorders, such as anxiety and depression. Maternal malnutrition during fetal development has a detrimental long-term impact on the physical, cognitive, and emotional development[142,143]. A deficit in maternal dietary protein during pregnancy alters the brain neurochemistry and behavior by reducing 5-hydroxytryptamine 1A receptor and the responsiveness to stress during adult life[144]. It has been shown that branched-chain amino acids such as leucine, isoleucine or valine are essential nutrients that promote resilience *via* activation of hippocampal BDNF signaling[145]. An unbalanced diet during pregnancy is linked to heightened HPA axis responses to stress and higher cortisol levels as well as epigenetic changes in genes controlling glucocorticoid action in adult offspring[146-148].

Microbiome and gut-brain axis: The gut microbiota plays a major role in shaping how the body responds to stress. Animal studies have shown that Germ-free mice with absent microbiota have significant variations in their stress response caused by abnormal development of the HPA axis that was reversed by inoculation of Bifidobacteria infantis[149]. Exposure to early life adversity is correlated with changes in microbial diversity of the gut where taxonomic abundances predicted PFC activity[150].

The microbiome-derived short-chain fatty acids (SCFA) are the most studied metabolites because they ameliorate the gut-brain axis and stress-induced cortisol release in humans and rodents[151]. The composition of diet is essential because it can impact gut-brain pathways involved in stress response. A healthy diet rich in fibers, phytochemicals, or live bacteria can increase microbial diversity and enhances production of SCFA and other bioactive compounds[152,153]. Western diet, lacking in dietary fibers, is associated with suboptimal gut microbiota composition and a low-grade systemic inflammation that can predispose to mental illness, gastrointestinal and metabolic disorders, and obesity[154,155]. In addition to diet, exercise has been shown to increase SCFA availability, thereby influencing microbiome composition[156]. Gut microbes also play a major role in synthesizing key neuroactive molecules such as serotonin, gamma-aminobutyric acid, and catecholamines like norepinephrine and dopamine. For example, *Lactobacillus* can stimulate the conversion of dietary tryptophan into 5-hydroxytryptamine by enterochromaffin cells, which then interacts with the autonomic nervous system and conveys the signal to other brain structures, such as the hypothalamus, nucleus accumbens, and ventral tegmental area [157-159].

Microbiome-targeted therapies known as "psychobiotics" that include administration of live organisms, fecal microbial transplants, and dietary interventions to reshape the microbiome composition and function have beneficial effects on brain and behavior[152,160,161]. Administration of the probiotic organisms *Bifidobacterium* and *Lactobacillus* is known to confer resilience in social defeat model and has been tested in clinical depression[161,162]. Additionally, probiotics supplementation results in higher DHEA-to-corticosterone fecal metabolite ratios and reduces microglia immunoreactivity in the basolateral amygdala in rodent models, thereby mitigating the pervasive effects of early life stress on anxiety and depressive behavior as well as HPA axis activity[163].

Modulating the microbiota–gut–brain-axis through diet is also a promising approach to prevent and treat mental health disorders. Consumption of a Mediterranean diet resulted in a significant improvement in depressive symptoms after 12 weeks of dietary intervention compared to control group among patients with major depressive disorder[164,165]. Studies have also shown that adherence to Mediterranean diet, consumption of fruits and vegetable-based dietary pattern and dietary polyphenols were positively associated with psychological resilience[166]. Polyphenols are stress-modifying phytochemicals composed of hydroxylated phenyl moieties and are abundant in fruits, vegetables, tea, caffeine, curcumin, herbs, citrus peel, and grape seeds. They have anti-inflammatory actions, which may be involved in fighting psychosocial stress. Therefore, polyphenols are considered adaptogens (stress response modifiers that have beneficial effects to protect from chronic diseases) because of their ability to adapt to and survive external stressors[167-171]. Polyphenols are also considered 'prebiotics' because of their ability to enhance the growth of specific beneficial bacteria that produce bioactive phenolic acids, which promotes cognitive resilience to depression and anxiety[172-175].

Exercise and resilience: Exercise is well known for its benefit in enhancing resilience and longevity. Physical activity through exercise activates endocrine, paracrine, and autocrine pathways through the release of exerkines (signaling particles that have a potential role in improving health in response to exercise), cytokines, nucleic acids, lipids, and metabolites from multiple organs[176]. Exercise is well known to improve brain function, most notably the effect on learning and memory. Indeed, aerobic exercise increases hippocampal volume and improves memory, increases plasma levels of BDNF, and delays the onset of neuro-degenerative conditions in older adults human studies[177-179]. These findings are in line with animal studies on rodents where chronic exercise resulted in upregulation of BDNF in the hippocampus, leading to hippocampal neurogenesis, neural plasticity, and improved cognition and mood[180]. A possible mechanism of the upregulation of BDNF in hippocampus is through the release of irisin from myokines, which plays an important role in hippocampal neurogenesis, increased neurotrophin levels, and enhanced mood and cognition[181]. Another benefit of exercise is the release of adiponectin from adipocyte that seems to have neuroprotective effects by crossing the blood–brain barrier and resulting in increased neurogenesis and reduced depression-like behaviors[182]. Kynurenic acid, another molecule of interest produced in muscles in response to chronic

aerobic exercise, has been shown to protect the brain from stress-induced depression[183]. Vigorous exercise is also associated with lower emotional distress, depression, and anxiety[184,185].

Studies have linked the adaptative changes in opioid systems to regular exercise, which reduces noradrenergic-induced stress responses. Regular exercise activates the endogenous opioid in the peripheral and central nervous system and is implicated in mood improvement[186,187]. The stress-reducing effect of exercise in response to both physical and psychological challenge is reversed by administration of naloxone, an opioid antagonist[188,189].

DISCUSSION

We have addressed in this minireview the biological basis of resilience as an outcome of structural and molecular alterations resulting from various determinants. Understanding the molecular aspect of resilience can provide insight for therapeutic discoveries and interventions to promote resilience in face of adverse life events. Here we showed that building resilience requires an intricate network of positive experiences and healthy lifestyle that contribute to a balanced mind-body connection (Figure 3). Indeed, positive childhood experiences such as interpersonal social and emotional support can mitigate the impact of adverse childhood experiences, thereby reducing the risk for adult onset depression and poor mental health[190].

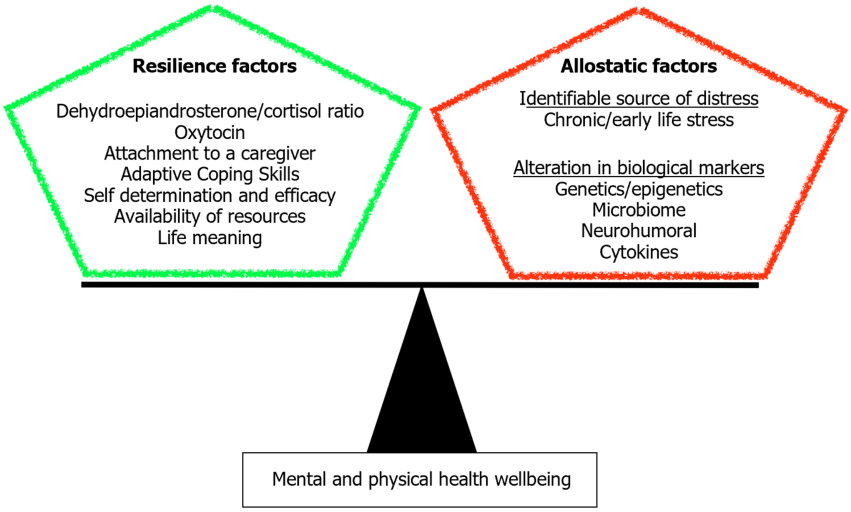
Clinical and preclinical investigations showed that resilience is implicated in molecular alterations and changes in brain regions involved with the social networks that promote empathy, social connectedness, and modulation of central responses to stress. DNA methylation in response to early life stress is potentially reversible through intervention. Resilience promoted by psychotherapy and mindfulness practices reverses the epigenetic modification of *FKBP5* and *BDNF* genes caused by stress response and alters cortical activation to improve PTSD symptoms[76-78,80,81]. Investigations also showed that DHEA-S, OXT and enhanced expression of MR can be used as important predictors of resilience[21,24,30]. OXT, a neuropeptide tied to attachment, plays a key role in promotion of postnatal sensitive maternal caregiving to optimize infant's social and emotional development and establish the neural networks needed during adult life to form social bonds[105-110]. OXT is also a feedback regulator of the HPA axis that enhance recovery from stress-related symptoms[114].

Recent studies also showed the association between early life adversities and circadian rhythm disruption as well as changes in brain-gut axis that may occur *via* pathways related to glutamatergic excitotoxicity and oxidative stress, predisposing to metabolic derangement, negative mood and stress [37,141]. Re-alignment of circadian rhythms to the natural light/dark cycle is an important health behavior that enhances resilience and adaptation to various stressors[41-43]. Additionally, a healthy brain-gut axis plays an important role in building resilience where gut microbial diversity, healthy diet and exercise can ameliorate the gut-brain axis and stress-induced cortisol release in humans and rodents. Administration of probiotics confer resilience in social defeat model and results in higher DHEA-to-corticosterone fecal metabolite[161,162], thereby mitigating the pervasive effects of early life stress on anxiety and depressive behavior as well as HPA axis activity[163].

Despite the advances in studying resilience and the multitude of contributing factors, there are still gaps in literature about genetic determinants that differentiate resilient individuals from vulnerable ones. Here we reviewed that epigenetic modification of *FKBP5* and *BDNF* genes in response to stress can be reversed by interventions to reduce stress[67,68]. Our group is currently conducting a large-scale study to determine what other genes are implicated in resilience in response to CCT psychotherapy. The advances in miRNA research can also be a powerful tool that can serve as a therapeutic target to improve resilience.

CONCLUSION

This minireview emphasized the dynamic process of resilience and showed that it continually evolves by the intersection of different domains in human's life; nature, nurture, environment, and microbiome. Despite the large number of research studies on resilience to stress, none have established one causal factor that differentiates a resilient person from a vulnerable one. This minireview demonstrated that a holistic approach, both clinically and for research purposes, must be adopted to address the multiple elements that promote resilience and prevent physical illnesses and psychopathology. Our future direction is to further understand the role of epigenetic gene silencing in chronic stress in order to identify potential resilience genes that can be reactivated by psychotherapy and the other resilience-promoting interventions mentioned above.



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Figure 3 Wellbeing as a measure of resilience and allostatic factors balanced output.

FOOTNOTES

Author contributions: Chbeir S and Carrión V conceived the manuscript idea; Chbeir S did writing and literature research; Carrión V did reviewing and editing.

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MINIREVIEWS

Neurobiological risk factors for problematic social media use as a specific form of Internet addiction: A narrative review

Sergey Yu Tereshchenko

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Abstract

Problematic social media use (PSMU) is a behavioral addiction, a specific form of problematic Internet use associated with the uncontrolled use of social networks. It is typical mostly for modern adolescents and young adults, which are the first generations fully grown up in the era of total digitalization of society. The modern biopsychosocial model of the formation of behavioral addictions, postulating the impact of a large number of biological, psychological, and social factors on addictive behavior formation, may be quite applicable to PSMU. In this narrative review, we discussed neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural/functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features. A review of the literature shows that the vast majority of the mentioned neurobiological studies were focused on computer games addiction and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU, there is practically no research on neuropeptide and genetic associations for PSMU to date. This fact points to the extremely high relevance of such studies.

Key Words: Internet addiction; Problematic social media use; Addictive behavior physiopathology; Neurobiology; Genetics

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Core Tip: The analysis of sources showed that the vast majority of neurobiological research was focused on the study of computer games addiction and generalized Internet addiction (without taking into account the content consumed). There is practically no research on neuropeptide and genetic associations for problematic social media use to date. This fact points to the extremely high relevance of such studies.

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INTRODUCTION

The last few decades have been characterised by the complete digitalization of society and the ubiquitous penetration of Internet technologies into our daily lives[1,2]. The advantages associated with the widespread introduction of Internet technologies into people's daily lives are undeniable (for example, quick access to a large amount of information and various services, rapid dissemination of news on a global scale, the introduction of Internet technologies related to health, *etc*.). However, a certain number of Internet users, mainly adolescents and young adults, experience the phenomenon of Internet addiction or "problematic/compulsive use of the Internet" which is associated with several psychosocial problems[2,3]. The global concern about the impact of problematic Internet use (PIU) from the public and social health points of view became especially acute during the coronavirus disease (COVID) pandemic when each person had to use the Internet more often, and initially, predisposed individuals were losing control, showed more and more signs of pathological addictive behavior when diving into the network[4]. In particular, this trend has affected the most technologically advanced segments of society – the first generations who grew up surrounded by the Internet and gadgets – adolescents and young adults[5]. The situation can be significantly aggravated by the neurophysiological consequences of the pandemic, predisposing to the development of depression and anxiety, which are important risk factors of problematic social media use (PSMU)[6].

The modern "component bio-psychosocial model" of behavioral addiction formation postulates an individual combination of genetic/biological, psychological, social, and cultural factors leading, in the case of PSMU, to overuse of social media and negative consequences (Figure 1).

In this narrative review, we shall discuss neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural/functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features.

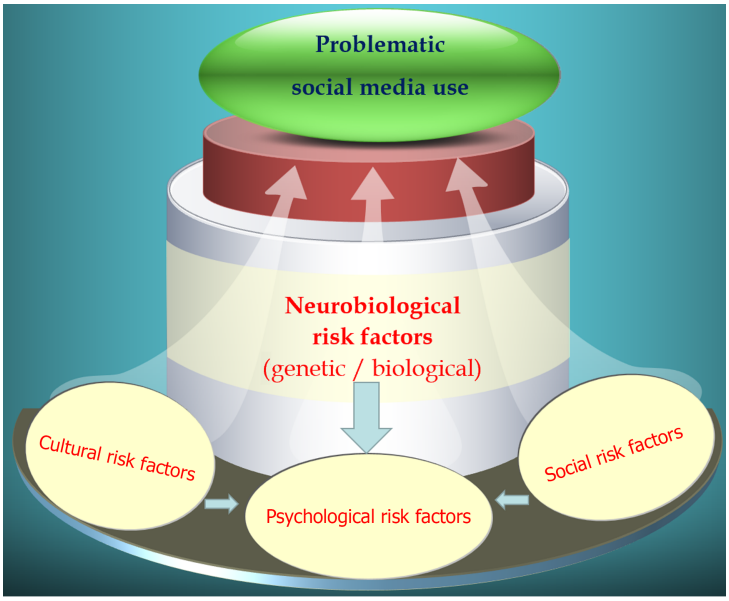
To find relevant publications, a search was conducted in PubMed, Scopus, Web of Science, and Reference Citation Analysis (https://www.referencecitationanalysis.com) for English-language sources using the following keywords and MeSH terms: "Internet addiction", "problematic social media use", "pathological social network use", "social media", "social networking", "specific Internet addiction", "video game addiction", "gaming disorder", "neurobiology", "behavior, addictive/physiopathology", "brain/physiopathology", "sympathetic nervous system", "parasympathetic nervous system", "neural pathways/physiopathology", "neurotransmitters", "biochemical correlates", "twin study", "genetics", "gene frequency", "genetic predisposition to disease", "polymorphism, single nucleotide".

TERMINOLOGY

The phenomenon of Internet addiction[7,8] was first described in the mid-1990s. There is currently no accepted formal definition of addictive online behaviour. Specialized literature offers such interchangeable terms as "problematic interactive media use"[9], "problematic Internet use", "pathological Internet use", "compulsive Internet use", and, finally, "Internet addiction". The European Network for Problematic Usage of the Internet (European research group) recommended in a recent review (2022) to use the term "problematic Internet use", as the most appropriate at this moment[4].

All of the above are umbrella terms, *i.e.*, reflect generalized (without reference to specific content and technology) PIU. Among the specific types of Internet activity, the following can be considered potentially addictive: Problematic video game use, PSMU, problematic Internet pornography use, Internet gambling, and web surfing addiction[10,11].

Only one of these five addictive behavior types, namely the problematic use of video games, is currently officially considered a mental disorder (Internet gaming disorder, diagnostic and statistical manual of mental disorders, fifth edition, American Psychiatric Association, 2013; gaming disorder, international classification of diseases-11, 2019). Recently, other specific forms of PIU have also been singled out: Online gambling disorder (it also includes intensive betting on online exchanges), online



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Figure 1 Component bio-psychosocial model of problematic social media use.

buying-shopping disorder, Internet streaming disorder, cyberchondria, cyberbullying, and digital hoarding[4].

PSMU is a behavioral addiction, a specific form of PIU associated with the uncontrolled use of social networks. It is typical mostly for modern adolescents and young adults, which are the first generations fully grown up in the era of total digitalization of society. There are currently no universally recognized and official criteria for the diagnosis of PSMU. The European Network for Problematic Usage of the Internet (European research group) suggests the following definition[4]: PSMU is a persistent state of control loss when using social networks, manifested by: Violation of control over interaction with social websites (for example, in terms of time, frequency, and duration of use); predominance of time spent on social networks over other life interests and activities; negative consequences, *i.e.*, the use of social networks leads to significant distress or deterioration in personal, family, social, educational, professional activities, or other important areas of functioning; continued or increased use of social networks, despite the negative consequences (for example, poor school performance, negative impact on health, social isolation, interpersonal conflicts, neglect of duties); duration, *i.e.*, the use of social networks can be continuous or episodic and repetitive but manifests itself over a long period (at least 12 mo).

Although the criteria for the diagnosis of PSMU are not formally established, the existing validation methods using questionnaires are based on the interpolation of classical symptoms for chemical and non-chemical types of addictive behavior[12]. Currently, there is a consensus on diagnostic criteria that clearly distinguish the pathological component of addiction from the normal daily use of the Internet by adolescents: The clinical diagnosis of PSMU, as well as generalized Internet addiction, should include six obvious signs[11,13,14]: Salience and mood modification, such as behavioral, cognitive, and emotional preoccupation: The growing importance of a social network for an adolescent in his or her system of interests and values; the use of a social network leads to a positive change in the emotional state; Compulsivity and loss of control: An obsessive desire to use the social network, impulsivity, loss of time control, excessive use of the social network (especially while reducing the allocated time for other activities); Tolerance: The need to spend more and more time communicating on a social network, including to alleviate episodes of dysphoria; Withdrawal/abstinence symptoms: Mood changes in the absence of access to a social network (depression, anxiety, aggressiveness); Conflict, impaired role performance: Loss of previous interests and entertainment, loss of educational, cultural, sports, and other opportunities as a result of excessive use of social networks; disputes and lies regarding the use of the social network; continued use of social networks, despite the negative consequences. Relapse: Rapid return to the use of the network after abstinence, unsuccessful independent attempts to control the use of the social network.

However, PSMU must be distinguished from intensive adaptive use of social networks. Adaptive intensive use of social networks itself does not have obvious negative consequences, has little effect on the parameters of well-being, and in many individual cases can play a positive role in the development of an adolescent by increasing a "social capital"[15-17].

PREVALENCE

The latest summarized data show that the average prevalence of PSMU among adolescents in 29 European countries is 7.4%[18]. The recent systematic review by Cheng *et al*[19] showed a high ethnic and geographic heterogeneity of PSMU prevalence within 5%–26%. The highest levels of PSMU prevalence are registered in collectivist societies in Asia and Africa[19]. Recent cross-national analysis of the psychometric characteristics from the social media disorder scale (SMDS) questionnaire among adolescents from 44 countries has shown high levels of validity and reliability (comparative fit index and Tucker–Lewis index = 0.963 and 0.951, root mean square error of approximation = 0.057)[20]. SMDS is recommended by the research group European Network for Problematic Usage of the Internet as preferred, since it evaluates primarily the psychopathological aspects of addiction, while the recently criticized Bergen social media addiction scale questionnaire does not clearly distinguish between simple excessive or prolonged use of social networks from pathological one, with signs of addiction[4]. The prevalence figures obtained by the authors of the SMDS were 7.3%-11.6% for the Dutch adolescent cohort[21]. Other studies using the SMDS have found similar results: 9.9%-10.0% in a Dutch sample in a longitudinal study[22], 9.4% in a representative sample of 3408 Finnish adolescents[23], and 8.0% in a large sample of Russian adolescents (n = 4514)[24].

PSYCHIATRIC AND SOMATIC COMORBIDITY

A large number of foreign studies have convincingly shown the pronounced comorbidity of Internet addiction with a wide range of psychopathological conditions. Depressive disorder and attention deficit hyperactivity disorder have the strongest association with Internet addiction, while anxiety disorder, obsessive-compulsive disorder; social phobia, and suicidal behavior also have a smaller but significant association[25-28]. A recent meta-analysis by Shannon *et al*[12] has shown that PSMU, as a specific form of Internet addiction, also reveals a moderate, but statistically significant, association with depression, anxiety, and stress[12]. Another recent meta-analysis demonstrated a significant but weak negative association of PSMU with life satisfaction and self-esteem (as parameters of well-being) and a moderate positive association with depression and loneliness (as indicators of distress)[29].

At present, not much is known about the association of Internet addiction with psychosomatic diseases, although such a connection is highly likely, given the presence of common pathogenesis factors (anxiety-depressive and obsessive-compulsive disorders). The study by Wei *et al*[30] based on an Internet survey demonstrated the association of Internet addiction with chronic pain syndromes, which the authors link with psychosomatic diseases and muscle overstrain. The study conducted by Cerutti *et al*[31] did not reveal a statistically significant association between Internet addiction and tension headache/migraine, although, in general, somatic symptoms were more often reported in the Internet addiction group[31]. In addition, it was discovered that PIU among adolescents was associated with chronic conditions, back pain, overweight, musculoskeletal pain, and also with sleep disorders[32,33]. According to a recent systematic review, a wide range of somatic health problems are associated with smartphone addiction among adults[34]. A general decrease in immune functions was observed in Internet-addictive individuals, which the authors link with a common risk factor, *i.e.*, stress, which can affect the activity of the sympathoadrenal axis and increase cortisol production[35]. It is characteristic that the high activity in the sympathetic part of the autonomic nervous system was detected when analyzing the heart rate of adolescents with Internet addiction[36,37]. A decrease in the quality of life, including the parameters of somatic health, was demonstrated in a systematic review by Masaeli and Billieux[38]. A pronounced connection between Internet addiction with the general level of somatization was revealed among young adults[39].

PATHOGENESIS OF INTERNET ADDICTION FROM A NEUROBIOLOGY POINT OF VIEW

To date, several etiopathogenetic models of the formation of Internet-dependent behavior among adolescents and young adults have been proposed[40]. Some researchers suggest the presence of mainly neurobiological risk factors linked with the lack of maturity in certain parts of the adolescent brain, which is manifested by insufficient effectiveness of volitional control, high impulsivity, and an overly activated brain reward circuitry[41,42]. However, the most recognized by researchers at present is the "component biopsychosocial model", which assumes a combination of psychosocial problems and neurobiological risk factors[40,43-45].

Middle and late stages of adolescence in brain development are characterized by different time frames of the formation of the limbic system and prefrontal cortex lobes[46]. The prolonged development of the prefrontal cortex in comparison with the limbic system during adolescence leads to weakened inhibition from cortex lobes concerning underlying subcortical structures and increased impulsivity, which contributes to a high risk of addictive behavior[47].

To date, a large number of studies have been devoted to the pathogenesis of Internet addiction using various neuroimaging techniques, including magnetic resonance imaging, positron and single photon emission computed emission tomography. These techniques have revealed a number of structural brain changes associated with Internet addiction[48-50]: Dcreased grey matter density in several areas, including prefrontal and orbitofrontal cortical layers and an additional motor area[51]; abnormal functional activity of brain regions associated with reward dependence[41]; activation of sensorimotor synchrony with a concomitant decrease in audiovisual synchrony[52]; activation of brain regions associated with compulsive craving and impulsivity; increased glucose metabolism in brain regions associated with impulsivity, reward dependence and the urge to repeat sensations[53]; increased dopamine secretion with a concomitant decrease in dopamine receptor availability in the striatum[54]. Meta-analysis of 40 neurophysiological studies of PIU has shown that, regardless of the content, Internet-dependent behavior is characterized by a significant violation of inhibitory control, stop-signal task, decision-making, and working memory[55]. The meta-analysis by Zhang *et al*[56] has revealed the presence of a common pattern in a brain structural change related to chemical and behavioral addictions: Changes in prefrontal and insula areas associated with increased impulsivity[56]. Several meta-analyses and reviews have been published recently: Structural and functional brain alterations for a specific form of PIU – computer games addiction[57-59]. The features of electroencephalography in Internet addiction were analyzed in a recent review by Sharifat and Suppiah[60]. Distinctive characteristics of functional electroencephalography were revealed among patients with computer game addiction[61].

It should be noted that most of the above-mentioned studies have been conducted for cases of computer games addiction or generalized (undifferentiated by the content consumed) Internet addiction. The recently proposed for various types of behavioral addictions updated interaction of person-affect-cognition-execution (I-PACE) model theoretically substantiates the neurobiological mechanism of addictive behavior, which consists in an imbalance between structures of frontostriatal circuits (limbic/reward-oriented brain circuits and prefrontal control)[62]. The model has been intensively studied for gambling and gaming disorders, but not for PSMU. Despite this, a line of structural and functional neuroimaging findings concerning the I-PACE model for PSMU was published to date[63-68]. Neuroimaging studies for PSMU were analyzed by Wegmann *et al*[69]; a conclusion was made about the significant association of PSMU with reward processing and reinforcement learning. A recent study by Sadeghi *et al*[70] has revealed that email addiction positively correlates with depression and gray matter volume of the left rostrolateral prefrontal cortex closely involved in cognitive processes[70].

There is some evidence of autonomic nervous system dysfunction involvement in the pathogenesis of Internet addiction, in particular, by the imbalance of the sympathetic and parasympathetic divisions[71, 72]. A general decrease in immune functions was revealed among Internet-addictive individuals. The authors link this fact with a common risk factor, *i.e.* stress, which can affect the activity of the sympathoadrenal axis and increase cortisol production[35]. The role of chronic stress in the formation of PSMU has been shown by several studies[12,73,74]. It is characteristic that the high activity of the autonomic nervous system's sympathetic part was observed when analyzing the heart rate of adolescents with Internet addiction[36,37]. Data on the level of cortisol for Internet addiction are contradictory[75-77]; additional research is required, in particular, concerning the long-term cortisol content, which can be a good marker of chronic stress and mental problems[78].

Several neurotransmitters and neurotrophic factors may be involved in the neurobiological mechanisms of Internet addiction formation[79-81]. Neurochemical pathways include metabolic disorders of dopamine, serotonin, opioids, and some other neurotransmitters that affect reward processing, executive functioning, salience attribution, and habit formation, as well as in the case of substance-use disorders[82]. The participation of these neurotransmitters is partially confirmed by the effectiveness of some pharmacological agents controlling the corresponding neurochemical pathways [83,84]. Exercise-based interventions also may be efficient for Internet addiction (including PSMU)[85], by regulating the autonomic nervous system, the morphology of some parts in the central nervous system, and the exchange of neurotrophic factors and neurotransmitters, in particular dopamine[72].

Oxytocin, which is called the hormone of trust, social connection, and emotional attachment, is promising for the PSMU study. It plays an extremely important role in establishing emotional social contacts, including those using social networks[80,86]. Bonassi *et al*[87] showed that a low level of parental care was associated with low activity on Instagram for carriers of the A-allele in the polymorphic region rs2254298 for the oxytocin receptor gene[87]. The same group of researchers identified a greater number of followers among carriers of the A/A genotype in the region rs53576 for the oxytocin receptor gene in comparison with carriers of the G-allele[88].

A significant number of studies show a pathophysiological relationship between the functioning of the oxytocinergic system and the formation of various forms of addictive behavior[89]. The effectiveness of exogenous oxytocin in the treatment of various addiction types has been shown both in experimental animal studies[90] and in a whole series of clinical studies[89]. It is assumed that the relief of physical symptoms and an increase in emotional tone during withdrawal, reduction of anxiety, increased susceptibility to verbal interventions, facilitating the restoration of social contacts, and, finally, the physiological reduction of established tolerance are the main mechanisms of oxytocin therapeutic

impact for chemical addictions. The hypothesis of oxytocin's antistress effect as a possible protective factor seems convincing since psychological stress is an important etiological cause of the development of pathological addictions[91].

The following are promising neurotransmitters and neurotrophic factors in addition to oxytocin, whose role in the pathogenesis of addictive Internet behavior in adolescents is also highly probable, but still insufficiently studied:

Melanocortin (α-Melanocyte-stimulating hormone). An important role of melanocortin in the development of pathological addiction is suggested by recent studies by Orellana *et al*[92]. There was a tendency to increase melatonin levels in the presence of computer games addiction[93];

Neurotensin. It is actively involved in the modulation of dopamine signalling and the formation of pathological addictions, attempts have been made to treat some addictions with synthetic neurotensin [94];

Orexin. It is supposed to be involved in the formation of sleep disorders and addictive behavior[95]. Choi *et al*[93] demonstrated an increase of orexin in the plasma of adolescents with Internet gaming disorder a while ago[93];

Substance P (neurokinin A). Impairment in the production of substance P is thought to be associated with the development of various pathological addictions; active attempts are currently being made to treat addiction by modulating the activity of neurokinin receptors[96,97];

Brain-derived neurotrophic factor (BDNF). This is a neurotrophic factor that plays a role in the development of addiction[98,99]. Data on the association of BDNF expression with Internet-addictive behavior are contradictory. Some authors found elevated plasma levels among addicts, the others did not confirm such an association[72,81]. A recent study by Choi *et al*[93], which has been mentioned above, found no direct link between addiction and BDNF levels, although it revealed a negative correlation with the time spent playing a computer game[93].

Glial cell line-derived neurotrophic factor (GDNF). It is a neurotrophic factor that plays an important role in supporting the function of dopaminergic neurons. A decrease in the level of GDNF in plasma was detected among Internet gaming addicts; besides, the expression of BDNF was negatively correlated with the severity of computer games addiction[100].

It is important to note that the vast majority of studies on neuropeptides and neurotrophic factors have been conducted for computer game addiction, as in the case of neuroimaging and neurophysiological research methods.

GENETICS OF INTERNET ADDICTION

Unlike other types of addictive behavior (for example, substance abuse or gambling), a very small number of studies have been devoted to the search for genetic predictors of Internet addiction. In the first twin study (2014) the authors managed to prove the presence of an innate component based on the results of a survey of 825 adolescents from the Chinese population. The component was estimated at 58%–66%[101]. Similar results were obtained a little later in the study of Turkish (19%–86%, 2014[102]) Dutch (48%, 2016[103]), Australian (41%, 2016[104]), and German (21%–44%, 2017[105]) twin cohorts. Positive genetic correlations (20%–40%, 2012) were also discovered in the study of various mobile phone use patterns by twins[106]. Although these data are limited by the volume of samples and various ethnic and geographic conditions, there is likely a tendency for a greater contribution of genetic factors in males.

Thus, the presence of a genetic component in Internet addiction formation has been convincingly shown by twin studies by the example of different populations, but no specific genes involved in the mechanisms of such heritability have been identified. Small pilot studies, however, verified polymorphic regions of nine candidate genes, the following are among those:

r1800497 [dopamine D2 receptor gene (*DRD2*), Taq1 A1 allele] and rs4680 [methionine variant of dopamine degradation enzyme catecholamine-o-methyltransferase gene (*COMT*)] – the first of such studies (2006–2007) conducted among adolescents in South Korea and showed an association between minor alleles connected with low dopamine production (rs4680) and a low number of dopamine receptors in the prefrontal cortex (rs1800497) with the presence of pathological Internet gaming disorder [107]. At the same time, *DRD2* A2 allele (high-activity) homozygotes and A1 allele (low-activity) carriers demonstrated no significant differences concerning Internet addiction; neither differences were revealed when comparing *COMT* high-activity (H) variant homozygotes and low-activity (L) variant carriers [108]. Later, the association of the C allele carrier rs1800497 (*DRD2* gene) with computer games addiction was confirmed for young adults[109]. Another study did not prove such a fact[110]. It is known that the *DRD2* gene is in linkage disequilibrium with the *ANKK1* gene, which plays a significant role in the formation of chemical addictions[111]. Therefore, by now, it is not possible to accurately establish the association of Internet addiction with the reception of dopamine at the DRD2 level[45]. The association of the homozygous variant Val/Val (GG) rs4680 (Val158Met, *COMT* gene) with addiction to computer games was further confirmed by the study by Yen *et al*[112] in 2022; In addition, a recent study by Kim *et al*[113] showed that the presence of interpersonal stress for *DRD2* rs6277 T allele and

rs1800497 Taq1 A1 allele showed higher scale values of computer games addiction[113].

rs6277 (promoter of the *DRD2* gene, *141C Ins/Del* polymorphism) – although a direct association between rs6277 polymorphism and Internet addiction has not been established, the *-141C* polymorphism may play a role in the pathogenesis of addiction as a mediator of temperament characteristics[110]; the dopamine D4 receptor gene (*DRD4* gene, VNTR polymorphism in exon 3) – as it was shown, the carriers of *DRD4* 4R/4R variants are more predisposed to the formation of generalized Internet addiction[108]. More recent studies have not shown an association with Internet-addictive behavior[114,115];

rs25531 (serotonin transporter gene (*SS-5HTTLPR*), short allelic variants) – the research by Lee *et al*[116] demonstrated that short allelic variants of the serotonin transporter gene might be associated with Internet addiction. Similar data were later obtained by Sun *et al*[108] but for men only[108]. As a large number of studies have shown, these genetic variants are also linked to a predisposition to depression, which is the most frequently detected comorbid condition among Internet-addictive individuals. Recent studies revealed that a link between depression and autistic personality traits with generalized Internet addiction could be modulated by such polymorphism (*5-HTTLPR*/rs25531), as well as ethnic and geographic factors[115,117].

rs1044396 [nicotinic acetylcholine receptor subunit alpha 4 gene (*CHRNA4*)] – study by Montag *et al*[118] revealed an association between Internet addiction and the rs1044396 CC genotype, which can also be associated with nicotine addiction and attention disorders. Later, Jeong *et al*[119] conducted a pilot study of the target exome, involving 30 adults with addiction to computer games and 30 healthy individuals, which included a study of 72 candidate genes. This study showed a statistically convincing association with one site only – rs1044396. No such association was found in another study[114];

rs2229910 [neurotrophic tyrosine kinase receptor type 3 gene (*NTRK3*)]– Kim *et al*[120] have conducted in turn a pilot study of the target exome involving 30 adults with addiction to computer games and 30 healthy individuals, which included a study of 83 polymorphic sites. Their study also revealed a statistically convincing association with one site only – rs2229910, presumably also associated with anxiety-panic, depressive disorders, obsessive-compulsive disorder, and psychologically determined eating disorders;

rs28364027 [Corticotropin Releasing Hormone Receptor 1 gene (*CRHR1*)] – a study involving Korean adolescent boys revealed that carriers of the AA genotype and the A allele were more predisposed to online computer games addiction[114]. It was previously determined that corticotropin-releasing hormone was involved in the mechanisms of negative effects realization when weaning from the addiction factor[121] and was associated with the risk of alcohol dependence for adolescents, especially when combined with stressful effects[122-124];

rs1137070 [monoamine oxidase-A gene (*MAOA*), EcoRV polymorphism] – the association of this polymorphism with an addiction to computer games with a mediator effect of hostility was evaluated for young adults. Participants with the TT rs1137070 genotype had a higher odds ratio of 2.52 (1.37-4.64) for gambling addiction compared with carriers of the C allele[125];

rs2268498 [oxytocin receptor gene (*OXTR*)] – it has been shown that male carriers of the TT genotype (but not female) have lower levels of generalized Internet addiction compared to C allele carriers[126];

rs6265 (*BDNF* gene) – Russian researchers discovered in 2019–2020 that genetic polymorphism of *BDNF* rs6265 (Val66Met), as well as the abovementioned *DRD4* exon 3 VNTR and *NTRK3* rs2229910, are were with the risk of generalized Internet addiction for young adults[127].

The latest (2022) review by Werling and Grünblatt[128] and the data presented in this article demonstrate that all currently known studies of genetic associations have been conducted for computer games addiction or (less often) for generalized Internet addiction. As far as is known, not a single study of genetic associations concerning PSMU has been published.

DISCUSSION

Neurobiology and genetics research on Internet-addictive behavior conducted over the last 10–15 years has allowed accumulating the necessary amount of knowledge to make certain intermediate conclusions, summarized recently in a significant number of meta-analyses and reviews. A large number of neuroimaging and neurophysiological studies have shown that Internet addiction is characterized by certain structural and functional features of the brain, accompanied by a significant violation of inhibitory control (increased impulsivity as a common factor in various forms of addictive behavior), stop-signal task, decision-making, and working memory. It has been discovered that, like other types of chemical and behavioral addictions, Internet addiction is characterized by an impairment of the metabolism of dopamine, serotonin, opioids, and some other neurotransmitters, which affects reward processing, executive functioning, salience attribution, and habit formation. A small number of pilot projects partially confirm the genetic basis of Internet addiction pathogenesis, previously demonstrated by twin studies.

An important aspect and trend in modern research on Internet-addictive behavior is an attempt to avoid the study of generalized, undifferentiated Internet addiction in favor of analyzing its specific

forms, such as computer games addiction and PSMU[24,129,130]. At the same time, the vast majority of the mentioned neurobiological studies were focused on computer games addiction (*e.g.* 85% of patients for functional magnetic resonance imaging[131]) and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU[66,67,69], there is practically no research on neuropeptide and genetic associations for PSMU to date. Attempts to use neuroimaging to look for common neurobiological mechanisms between PSMU and other addictions have so far produced conflicting results, at least in relation to the prefrontal cortex[66,67,132-134].

Although studies of generalized Internet addiction – especially for women – can be partially extrapolated to PSMU (taking into account common gender and psychosocial characteristics for some populations[24]), it is extremely important to study the directly verified PSMU, which differs significantly from computer games addiction. Further research is needed to better identify commonalities and differences in the neurobiology of different types of addictive online behavior in the context of the content consumed, the devices and technologies used, and the stability of symptoms across age. The study of neuropeptides directly involved in social bonding: Oxytocin and vasopressin, as well as orexin, melatonin, and neurotrophic factors (BDNF and GDNF), looks promising for PSMU neuromolecular associations.

Genetic studies conducted on small samples, conflicting and still quite scarce, should also be expanded to specific forms of Internet addiction, such as PSMU and smartphone addiction. Replication studies with a large number of participants are urgently needed, as well as genome-wide association and polygenic risk score estimate projects.

CONCLUSION

In this narrative review, we discussed neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural/functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features. A review of the literature shows that the vast majority of the mentioned neurobiological studies were focused on computer games addiction and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU, there is practically no research on neuropeptide and genetic associations for PSMU to date. This fact points to the extremely high relevance of such studies.

FOOTNOTES

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Deep brain stimulation for autism spectrum disorder

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Abstract

Deep brain stimulation (DBS) is a medical treatment that aims to obtain therapeutic effects by applying chronic electrical impulses in specific brain structures and neurological circuits. Over the years, DBS has been studied for the treatment of many psychiatric disorders. Scientific research on the use of DBS in people with autism has focused this interest mainly on treatment-resistant obsessive-compulsive disorder, drug-resistant epilepsy, self-injurious behaviors (SIB), and aggressive behaviors toward the self. Autism spectrum disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, and cognitive skills and the presence of repetitive and stereotyped behaviors as well as restricted interests. People with autism often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers. Obsessive-compulsive symptoms can be found in up to 81.3% of people with autism. They are often severe, refractory to treatment, and particularly difficult to treat. SIB has a high prevalence in severely retarded individuals and is often associated with autism. Drug treatment of both autism and SIB presents a therapeutic challenge. To describe the current state of the art regarding the efficacy of DBS in people with ASD, a literature search was conducted for relevant studies using the PubMed database. Thirteen studies have been considered in this paper. Up to date, DBS has been used for the stimulation of the nucleus accumbens, globus pallidus internus, anterior limb of the internal capsule, ventral anterior limb of the internal capsule, basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle, and posterior hypothalamus. In the total sample of 16 patients, 4 were adolescents, and 12 were adults. All patients had symptoms resistant to multiple drug therapy. Many patients taken into consideration by the studies showed clinical improvements as evidenced by the scores of the psychopathological scales used. In some cases, clinical improvements have varied over time, which may require further investigation. Among the new therapeutic perspectives, DBS could be a valid option. However, further, and more in-depth research is needed in this field.

Key Words: Deep brain stimulation; Autism spectrum disorder; Comorbidities; Drug

resistant; New therapeutic perspectives

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Core Tip: Deep brain stimulation (DBS) is a medical treatment that aims at obtaining therapeutic effects by applying chronic electrical impulses in specific brain structures and neurological circuits. Autism spectrum disorder comprises a group of developmental disabilities that are often associated with numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers. Comorbidities often require multiple drug treatments with an increasing rate of treatment resistance. Thirteen studies have been considered in this paper. Up to date, DBS has been used for the stimulation of the nucleus accumbens, globus pallidus internus, anterior limb of the internal capsule, ventral anterior limb of the internal capsule, basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle, and posterior hypothalamus. In the total sample of 16 patients, 4 were adolescents (all males), and 12 were adults (5 males and 7 females). All patients had symptoms resistant to multiple drug therapy. Only one patient was considered not a responder to DBS. Among the new therapeutic perspectives, as evidenced by the studies presented in this article, DBS could be a valid option. However, further, and more in-depth research is needed in this field.

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INTRODUCTION

Deep brain stimulation (DBS) is a medical treatment that aims at obtaining therapeutic effects of certain neurological and psychiatric disorders by applying chronic electrical impulses in specific brain structures and neurological circuits[1]. The modern beginning of DBS can be traced back to the work of Benabid, Pollak, and colleagues at the Joseph Fourier University in Grenoble in the 1980s[2], based on several decades of clinical work and biophysical discoveries[3]. The clinical success of DBS has opened the door to other neurostimulation therapies such as transcranial magnetic stimulation and has motivated an intense analysis of the neural circuits affected by neurological disorders such as Parkinson's disease[4]. The first use of DBS for a psychiatric indication was published by Nuttin *et al*[5] in 1999. Over the years, DBS has been studied for the treatment of obsessive-compulsive disorder (OCD)[6], tardive dyskinesia (TD)[7], treatment-resistant depression[8-10], Tourette's syndrome[11], treatment-refractory anorexia nervosa[12].

Autism spectrum disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, cognitive skills and the presence of repetitive and stereotyped behaviors as well as restricted interests[13]. In addition to core symptoms, people with ASD often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers[14]. Obsessive-compulsive symptoms can be found in up to 81.3% of people with ASD. They are often severe, refractory to treatment, may be clinically confused with core symptoms of ASD, and are particularly difficult to treat[15,16].

Self-injurious behavior (SIB) has been defined as "behavior which produces physical injury to the individual's own body"[17]. SIB has a high prevalence in severely retarded individuals and is often associated with autism. Indeed, up to 42% of people with autism may exhibit repetitive SIBs[18]. Additionally, over 75% of children with SIB will have these behaviors persist into adulthood sometimes resulting in serious harm and even death[19-21].

In approximately two-thirds of cases, SIB is maintained by social variables[22], while in approximately one-quarter of cases, SIB occurs independently of social consequences [automatic reinforcement subtype, automatically maintained SIB (ASIB)][23]. ASIB is considered the most challenging subtype to treat, because the events that cause and maintain it are not known. Currently, ASIB is classified into three subtypes[24,25]. Subtype 1 ASIB is characterized by higher rates of SIB in conditions with minimal external stimulation. Subtype 2 ASIB is characterized by high or variable rates of SIB across high and low stimulation conditions. Subtype 3 ASIB is characterized by the presence of self-restraint[26].

Drug treatment of both autism and SIB presents a therapeutic challenge. Some drugs such as risperidone, aripiprazole, and fluoxetine have shown positive efficacy evidence for treating irritability in people with ASD but not for specifically reducing self-harm[27-30]. Currently, the most successful therapeutic strategies for SIBs are based on applied behavioral analysis techniques[31,32] combined

with pharmacological treatments with neuroleptics, mood stabilizers, sedatives, but some patients remain refractory[33].

The present work aims to describe the current state of the art regarding the efficacy of DBS in people with ASD.

A literature search was conducted for relevant studies using PubMed database. In drafting this paper, the authors decided to consider the published articles, classifying them according to the brain regions stimulated by DBS and not according to the pathologies treated.

There are clinical studies on animal models in the literature, but in this article, we will only consider human clinical studies, as we are more interested in the usefulness and efficacy of DBS in clinical practice.

Scientific research on the use of DBS in people with autism has focused this interest mainly on treatment-resistant OCD, drug-resistant epilepsy (DRE), SIBs, and aggressive behaviors toward self. Four studies in the literature have used DBS to treat OCD and other comorbidities in people with ASD [34-37] (see Table 1). Five studies investigated the efficacy of DBS in the treatment of SIB in people with autism[38-42]. A protocol for the application of DBS in children and young adults has recently been published, but the results are not yet available[43]. Furthermore, Heiden *et al*[44] published a retrospective study of the use of DBS in ten patients, including two patients with autism, but the results were not extrapolated for the different pathologies. This makes it impossible to consider the efficacy of DBS in the autistic patients included in the study. Torres *et al*[45] also published a study on the use of DBS for aggression in 7 patients, 5 of whom had autism. The results were not divided for a single patient not allowing to identify of the efficacy of DBS for autistic patients. Recently Benedetti-Isaac *et al* [46] published a follow-up study on the use of DBS in 5 pediatric autistic patients with aggressive behaviors resistant to drug therapy, but the results were not divided by single patient.

In the total sample of 16 patients, 4 were adolescents (all males), and 12 were adults (5 males and 7 females). All patients had symptoms resistant to multiple drug therapy. Generally, treatment resistance consists of three core components: Correct psychiatric diagnosis, adequate treatment, and symptoms not responding adequately despite treatment[47].

USE OF DBS IN PEOPLE WITH AUTISM

In patients with autism, the literature published so far has used DBS for the stimulation of the nucleus accumbens (NAc), Globus Pallidus internus (GPi), anterior limb of internal capsule (ALIC), ventral ALIC (vALIC), basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle (MFB), posterior hypothalamus (PHyp).

Three studies[33,34,39] have applied DBS to the NAc of people with autism and numerous comorbidities. Past literature has shown that the NAc may be a key structure for the control of OCD symptoms[48,49], in modulating aggression[50], and in improving the response to social stimuli in ASD [51].

Segar *et al*[34] showed the efficacy of DBS in a 24-year-old female patient with Kleefstra Syndrome with comorbidities of ASD, OCD, and Tourette-like symptoms. The clinical improvements mainly concerned the patient's compulsive behaviors, coprolalia, language, and social interaction, with marked improvement in the global assessment of functioning scores.

In 2019, Doshi *et al*[35] reported a 42-year-old woman with autism who underwent bilateral NAc DBS for control of severe OCD and aggression (violent outbursts against others and hitting and injuring others and herself) refractory to pharmacological treatments. In the days following the surgery, the patient had shown a marked difference in her behavior and eye contact, and appropriate laughter. Clinical improvements were consistent with improvements in administered psychopathology scale scores [Yale-Brown obsessive-compulsive scale (Y-BOCS), Hamilton depression scale, Hamilton anxiety scale, and social communication questionnaire].

Park *et al*[40] observed remarkable clinical improvements in a 14-year-old boy with ASD and SIB treated with bilateral NAc DBS. The clinical improvements (assessed with the Y-BOCS, clinical global impression scale, attention deficit hyperactive disorder rating scale, and social responsiveness scale), were accompanied by functional and structural changes in the brain after DBS, demonstrated using fluorodeoxyglucose positron emission tomography/computed tomography imaging. Furthermore, at the 2-year post-operative evaluation, the boy showed improved language comprehension and expression skills, and improved eye contact.

Two studies[38,41] have applied GPi DBS to people with autism to improve movement impairments. Stocco *et al*[39] applied GPi DBS to two people with ASD, severe stereotypies, and SIB (one patient simultaneously received DBS in GPi and the Anterior limb of the internal capsule). Only the patient who received GPi DBS had maintained clinical improvements over time, even reducing drug therapy. As suggested by the authors, GPi DBS may provide relief for severe pharmacologically unresponsive stereotypies in some patients. Indeed, the characteristics of the ideal patient to be subjected to DBS should be better explored.

Table 1 Summary of deep brain stimulation studies for autism spectrum disorder

Ref.	Patients' age/sex	Diagnosis and comorbidities	Indications for DBS	DBS targets	Pre-BDS scores	Post-BDS scores	Main outcomes
Segar *et al*[34]	24, F	KS, OCD, ASD, epilepsy	Biting hands, picking skin	NAc	GAF 20	GAF 50-60	Clinical improvements mainly for compulsive behaviors, coprolalia, language and social interaction
Doshi *et al*[35]	42, F	OCD, ASD, epilepsy	OCD, aggression	NAc	Y-BOCS 19, HAMD 20, HAS 30, SCQ 26	Y-BOCS 5, HAMD 15, HAS 18, SCQ 16	Marked improvements in OCD symptoms, aggressive behavior, eye contact and appropriate laughter
Park *et al*[40]	13, M	ASD, Develop-mental Delay	Self-mutilation, face-hitting	NAc	CGI-S 6; ABC 106; CY-BOCS 22; K-ARS 54; SRS 101	CGI-S 4; ABC 40; CY- BOCS 7; K-ARS 36; SRS 98	Decreased in SIB and improvement in verbal communication
Stocco *et al* [39]	19, F	ASD, ID, monosomy 2q and trisomy 20p	Self-picking, Severe stereotypes	GPi	JHMRS 46	JHMRS 4	Marked improvement in the SIB and dystonia
	17, M	ASD, ID, anxiety	Punching of arms and legs, biting, Severe stereotypes	GPi and ALIC	JHMRS 67	JHMRS 19	Substantial initial improvement in SIB, but the benefit disappeared after 6 mo and was not regained
Kakko *et al* [42]	19, M	ASD, ID, epilepsy, TD	Aggression, self-mutilation, lacerations	GPi	NR	NR	TD symptoms were markedly improved. The anxiety, behavioral symptoms had ceased
Sturm *et al*[38]	13, M	Kanner's Autism, ID, infantile cerebral palsy	Self-aggression	Basolateral amygdala	Parental score of 6	Parental score of 2	Decreased in SIB and core symptoms of the autism spectrum in the emotional, social, and cognitive domains
Davis *et al*[36]	44, M	OCD, ASD, MDD, tics, epilepsy	OCD, aggression	Ventral capsule/ventral striatum	Y-BOCS, MADRS, YGTSS	Y-BOCS, MADRS and YGTSS scores decreased by 68%, 66%, and 75% respectively	The clinical improvements were maintained, albeit with fluctuations, after 3 yr. No effect on core symptoms of ASD
Graat *et al*[37]	39, F	OCD, ASD, Depressive episodes	OCD	vALIC	Y-BOCS 33, HAMD 27	Y-BOCS 12, HAMD 7	50% reduction of OCD symptoms following DBS, especially obsessions
	54, F	OCD, ASD	OCD	vALIC, then MFB	Y-BOCS 38, HAMD 30	Y-BOCS 18, HAMD 4	Initially did not benefit from DBS. Thereafter OCD symptoms improved and decreased by more than 50%
	32, M	OCD, ASD, ADHD	OCD, aggressive intrusions	vALIC	Y-BOCS 31, HAMD 18	Y-BOCS 23, HAMD 12	Partial responder probably due to several transient side effects of DBS
	31, F	OCD, ASD, DD, OCPD, AN	OCD	vALIC	Y-BOCS 34, HAMD 30	Y-BOCS 32, HAMD 27	Only some subjective improvements
	51, M	OCD, ASD	OCD	MFB	Y-BOCS 34, HAMD 5	Y-BOCS 0, HAMD 2	Obsessive-compulsive symptoms disappeared entirely. Improved confidence and less social

							shyness
	30, F	OCD, ASD, PDD, GAD, UPD	OCD,	MFB	Y-BOCS 34, HAMD 23	Y-BOCS 22, HAMD 22	35% reduction of OCD symptoms following DBS
Benedetti-Isaac *et al*[41]	27, M	ASD, TBI, epilepsy	Aggressive behavior towards self	PHyp	OAS 9	OAS 1	Improvements in seizures, in aggressive behavior, in quality of life, in daily living skills
	16, M	ASD, epilepsy, Developmental Delay	Self-aggression	PHyp	OAS 8	OAS 1	Aggressive behavior controlled for a month. After 2 mo it reappeared as before surgery

ABC: Antecedent, behavior, consequence; ADHD: Attention deficit hyperactive disorder; ALIC: Anterior limb of internal capsule; AN: Anorexia nervosa; ASD: Autism spectrum disorder; CGI-S: Clinical global impressions-severity; CY-BOCS: Children's Yale-Brown obsessive-compulsive scale; DBS: Deep brain stimulation; DD: Depressive disorder; F: Female; GAD: Generalized anxiety disorder; GAF: Global assessment of functioning; GPi: Globus Pallidus internus; HAMD: Hamilton depression scale; HAS: Hamilton anxiety scale; ID: Intellectual disability; JHMRS: Johns Hopkins motor stereotypy rating scale; K-ARS: Korea attention deficit hyperactive disorder rating scale; KS: Kleefstra syndrome; M: Male; MADRS: Montgomery-Asberg depression rating scale; MDD: Major depressive disorder; MFB: Medial forebrain bundle; NAc: Nucleus accumbens; NR: Not reported; OAS: Overt aggression scale; OCD: Obsessive-compulsive disorder; OCPD: Obsessive-compulsive personality disorder; PDD: Persistent depressive disorder; PHyp: Posterior hypothalamus; SCQ: Social communication questionnaire; SRS: Social responsiveness scale; TBI: Traumatic brain injury; TD: Tardive dyskinesia; UPD: Unspecified personality disorder; vALIC: Ventral anterior limb of the internal capsule; Y-BOCS: Yale-Brown obsessive-compulsive scale; YGTSS: Yale global tic severity scale.

Tardive dyskinesia (TD) is probably the most severe form of extrapyramidal symptoms (EPS) secondary to antipsychotic drugs, manifesting usually after months or years of therapy with involuntary choreiform movements and dystonia, frequently affecting the face and tongue[52]. While there are drug treatments for TD, it is often chronic and irreversible. Furthermore, patients with intellectual disabilities (ID) are more susceptible to EPS[53]. Past literature has shown encouraging evidence of DBS in the treatment of dystonic cerebral palsy in children[54]. GPi DBS in a young adult diagnosed with ASD and ID markedly improved TD symptoms[42]. The anxiety, restlessness, behavioral symptoms, and self-destructive behavior have ceased. Furthermore, the patient's skills, especially communication skills, have returned to the level before the presentation of aggressive seizures.

In 2013 Sturm *et al*[38] treated a 13-year-old boy with ASD and SIB with DBS in the amygdaloid complex and supra-amygdaloid projection system. The implantation of the electrodes in the two areas had been made necessary to testify that possible mechanical irritations, micro-lesions or inflammations in the projections of the amygdala were not effective in controlling the symptoms. Only stimulation of the basolateral nucleus of the amygdala proved effective in improving self-harm and core symptoms of ASD in the emotional, social, communicative, and cognitive domains in a 24-mo follow-up.

Davis *et al*[36] subjected a 44-year-old man with treatment-resistant OCD, major depressive disorder, ASD, and tics to DBS. DBS targets were represented by the ventral capsule and ventral striatum. After 3 years, the clinical improvements obtained within 6 mo of the surgery were maintained, albeit with fluctuations. Indeed, the scores on the Y-BOCS and the Montgomery-Asberg depression rating scale indicated that his symptoms were in the mild range, while the scores on the Yale global tic severity scale were much improved. On the other hand, as expected by the authors, full resolution of symptoms was never achieved and the patient continued to experience the clinical features of ASD.

In 2022, Graat *et al*[37] published the results of six patients with refractory OCD comorbid with ASD who underwent DBS of the vALIC or MFB. The efficacy of DBS on obsessive-compulsive and depressive symptoms was tested with the Y-BOCS and the Hamilton depression rating scale, respectively. Considering Y-BOCS scores, four patients were responders (> 35% decrease Y-BOCS), one patient was a partial responder (25%–35% decrease Y-BOCS) probably due to transient side effects of DBS, and one patient was a non-responder (< 25% decrease Y- BOCS), even though she had subjective symptom improvements.

After considering previously published studies[55,56] on the evidence of surgical treatment of the PHyp in aggressive drug-resistant behaviors, Benedetti-Isaac *et al*[41] published the results of PHyp DBS in 5 patients with DRE associated with intractable aggressive behavior. Only two patients among those recruited were also affected by ASD. A 27-year-old man with ID associated with severe autism, reported improvement in quality of life, better access to special education, and improvements in daily living activities. On the other hand, the aggressive behavior of a 16-year-old boy with ID and severe autism, was partially controlled for a month, but after 2 mo it reappeared as before surgery despite stimulation.

Only one study[37] reported adverse effects of DBS. One patient showed severe transient side effects: an infection of the DBS system that required removal of the system and, at a later stage, a suicide attempt (overdosed of quetiapine). Suicidality resolved without changing stimulation settings. Other

transient adverse effects were represented by restlessness, hypomania, tics, impulsivity, agitation, forgetfulness, cramp/joint pain, headache, memory complaints, agitation, hallucinations, and delusions.

CONCLUSION

The multiple comorbidities associated with ASD and the drug resistance in some patients lead to a decrease in the quality of life of patients and their family members or caregivers. To date, DBS has been used in people with autism solely to treat comorbid conditions. Despite encouraging results for the treatment of drug-resistant diseases, positive effects on core symptoms of ASD have only occasionally been reported. Finding new and innovative treatments is a fundamental aspect for those who take care of people with autism and comorbid conditions resistant to conventional treatments. Among the new therapeutic perspectives, as highlighted by the studies presented in this article, DBS could be a valid option to improve the management of disabling pathologies comorbid with autism and consequently the quality of life. However, further, and more in-depth research is needed in this field.

FOOTNOTES

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MINIREVIEWS

Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: A literature review

Lakshan N Fonseka, Benjamin KP Woo

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Abstract

With the Food and Drug Administration designation in 2017 of 3,4-methylenedioxymethamphetamine (MDMA) as a breakthrough therapy in post-traumatic stress disorder and psilocybin in treatment-resistant depression, psychedelic drugs have continued to garner the attention of researchers and clinicians for their promise of unmatched, rapid improvement in a multitude of psychiatric conditions. Classic psychedelic drugs including psilocybin, lysergic acid diethylamide, and ayahuasca, as well as non-classic drugs such as MDMA and ketamine, are currently being investigated for a potential therapeutic role in trauma, depressive disorders, and other psychopathologies. However, psilocybin and MDMA each have a functional profile well-suited for integration with psychotherapy. The present review focuses on psilocybin and MDMA in psychedelic-assisted therapy (PAT), as these studies compose most of the literature pool. In this review, we discuss the current and future uses of psychedelic drugs, with an emphasis on the role of MDMA and psilocybin in PAT in the setting of trauma and related comorbidities on the efficacy of psychedelic drugs across multiple psychiatric disorders. The article concludes with thoughts for future research, such as incorporating wearables and standardization of symptom scales, therapy styles, and assessment of adverse drug reactions.

Key Words: Psychedelics; Trauma; Depression; Methylenedioxymethamphetamine; Ecstasy; Psilocybin

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Core Tip: Psychedelic-assisted therapy with psilocybin or 3,4-methylenedioxymethamphetamine (MDMA) is strongly supportive across psychiatric conditions, especially trauma and related comorbidities, as demonstrated through a pattern of rapid and sustained symptom relief. Both treatments seem to have benefits beyond the Food and Drug Administration breakthrough designations of treatment-resistant depression for psilocybin and post-traumatic stress disorder for MDMA.

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INTRODUCTION

The psychedelic renaissance of modern psychiatry can trace its resurgence to 2017-2018, when the Food and Drug Administration (FDA) designated breakthrough therapy status to psilocybin in treatment-resistant depression and 3,4-methylenedioxymethamphetamine (MDMA) in post-traumatic stress disorder (PTSD). Psychedelics can be broadly categorized as classic psychedelics that act as agonists at the 5-HT_{2A} receptor [*i.e.*, psilocybin, lysergic acid diethylamide (LSD), ayahuasca/dimethyltryptamine], empathogens that increase serotonin levels (*i.e.*, MDMA), antagonists at N-methyl-D-aspartate receptors (*i.e.*, ketamine), and atypical hallucinogens with effects across neurotransmitter systems[1,2]. Psychedelic-assisted psychotherapy (PAT) involving MDMA or psilocybin composes most of the literature pool, though studies involving other psychopathologies and compounds have also been investigated to a lesser extent. The predominance of both psilocybin and MDMA in the literature may be attributed to the properties that make each an ideal adjunct to psychotherapy.

Psilocybin and its active metabolite psilocin are derived from psychoactive mushroom species originally used in ceremonial settings to facilitate spiritual experiences in Central and South America, later introduced to Western culture in the 1950s[1,3]. As a classic psychedelic, psilocybin is a 5-HT_{2A} receptor agonist that was found to produce rapid yet enduring improvement in treatment-resistant depression and major depressive disorder (MDD)[4-6]. More recently, psilocybin was compared to escitalopram in a double-blind trial. Both treatments were found to have similar efficacy in depression, which will be discussed in more detail in the present article[7].

Psilocybin further enhances its synergism with psychotherapy by evoking a sense of unity, ego-dissolution, and awe through "mystical" experiences[8-10]. As described by Vaid *et al*[11] (2022), PAT may enable the processing of emotional experiences that were previously inaccessible due to trauma blocks. This promotes reconnection with the self and "foundational identity deficit repair," a re-stabilization of the core ideas that together represent the conscious identity, self-esteem, and other aspects of the self[11]. As will be described later in this article, patients in recent studies report significant reductions in symptom rating scales, with benefits partly attributed to this mystical component-experiences of oneness or ego-dissolution, connection to self-essence, and a broadened perspective beyond self-imposed limits on thought processes and rigid mental frameworks that may once have been adaptive responses to life events[12,13].

MDMA was initially developed by Merck & Co. for hemostasis in 1912, and its psychoactive effects were not published until 1978. After becoming popularized as recreational drug "ecstasy" in the 1980s [1,14,15], the Drug Enforcement Agency cited concerns of abuse potential and neurotoxicity and assigned schedule I status to MDMA in 1985. MDMA is part of a class of psychedelics, termed empathogens or enactogens, that increase empathy and social connection. Its effects are primarily mediated by serotonergic activity, including serotonin/norepinephrine transporter reuptake inhibition and partial agonism of serotonin receptors (5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C})[1]. By far, MDMA studies formed most of the research elicited by the PubMed search terms. The reasons for the clear bias in the literature and its consequences are varied and discussed in the future directions section. Nevertheless, the research has yielded promising results across psychopathologies, though most research aligns with its FDA designation for PTSD. A recent double-blind, phase 3 clinical trial found that 67% of participants receiving MDMA-assisted psychotherapy no longer met PTSD criteria after 2 mo[16]. These improvements are attributed to several downstream changes in cognition that further complement psychotherapy.

MDMA has been previously shown to decrease amygdala response when patients are presented with angry faces, as well as increase ventral striatum response when viewing happy faces, further supporting that MDMA reduces threat response, enhances reward, and facilitates positive social interactions[1,17,18]. MDMA has the reputation of generating feelings of closeness, connection, and emotional empathy, although similar features also exist in classic psychedelics[19,20]. However, MDMA uniquely offers augmentation of the therapeutic alliance, easefully lowering barriers and enabling the patient to process traumatic memories without feeling overwhelmed[1,21].

MDMA, psilocybin, and other psychedelics appear to induce a temporary period of increased neuroplasticity with associated changes in psychological flexibility[21,22]. Psilocybin studies have demonstrated increased neurogenesis, spinogenesis, and synaptogenesis that facilitate the reconditioning of fear memory and the reversal of stress-induced changes to the prefrontal cortex[23-25]. The plasticity counters the deficits in fear memory extinction seen in PTSD, alleviating distress from the cycle of avoidance and flashbacks associated with persistent traumatic memories[26-28]. Kéri *et al*[29] suggest that psychedelic-induced serotonin-glutamate interactions affect memory pathways responsible for memory destabilization and reconsolidation[29]. The neuroplastic and fear memory changes enrich the benefits drawn from combination with psychotherapy.

The present focus is on psychedelics involved in PAT, namely MDMA and psilocybin as these studies compose much of the literature pool. A literature review was conducted through PubMed database search of ((psilocybin) OR (MDMA)) AND (trauma). The search was also performed on Reference Citation Analysis (https://www.referencecitationanalysis.com/). The aim is to summarize the literature on psychedelic drugs, with an emphasis on the role of MDMA and psilocybin in PAT in the setting of trauma and related depressive disorders, from 2020 to 2022, bridging the gap from Reiff *et al*'s review encompassing articles from 2007 to 2019 on the efficacy of psychedelic drugs across multiple psychiatric disorders[1]. The article concludes with thoughts for future research, such as incorporating wearables and standardization of symptom scales, therapy styles, and assessment of adverse drug reactions.

PSILOCYBIN

With its FDA designation for treatment-resistant depression, it follows to begin the discussion of psilocybin with updates in depression, a common comorbidity in trauma-related conditions. Carhart-Harris *et al*[7] published a clinical trial comparing psilocybin *vs* escitalopram in 59 patients with MDD [7]. The psylocibin group (n = 30) received 25 mg of psilocybin at the start and a second dose at 3 wk, all while receiving 6 wk of daily placebo. The escitalopram group (n = 29) received 1 mg of psilocybin at the start and a second dose of 1 mg at 3 wk, with daily oral escitalopram 10 mg throughout the 6-wk study. The primary outcome measure was changes from baselines scores (range 0 to 27) on the quick inventory of depressive symptomatology (QIDS-SR-16), with a response defined as reduction in score of at least 50% and remission defined as a score of 5 or less.

A response occurred in 70% of the psilocybin group and 48% of the escitalopram group, while remission occurred in 57% of the psilocybin group and 28% of the escitalopram group. Although these differences do not reach significance, it is notable that both psilocybin and escitalopram appear, at a minimum, to have equivalent impacts. The lack of control group prevents the comparison of each treatment to a baseline population, but it is promising that the efficacy is similar between psilocybin and escitalopram. The authors report that while the initial trial design included a placebo group, this became too practically complex and expensive. Other limitations of the study include the duration, as escitalopram may require more time to display its full efficacy. Additionally, the patients in the trial were not from varying socioeconomic or ethnic backgrounds, limiting external validity. The study also included many secondary outcomes, including scores on other symptom scales, but these were not considered useful as the data were unadjusted for multiple comparisons.

Further analysis of the study was conducted by Murphy *et al*[30] regarding the influence of therapeutic alliance. It was found that increased strength of therapeutic alliance led to greater emotional breakthrough and mystical experiences across two PAT sessions[30]. Interestingly, the average symptom severity scores at baseline were in the range for moderate depression[7], highlighting an additional application for psilocybin beyond treatment-resistant depression.

In a patient population with moderate to severe MDD, Davis *et al*[31] performed an 8-wk intervention consisting of two psilocybin dosing sessions less than two weeks apart with supportive psychotherapy. Exclusion criteria illustrate the reduced the severity of depression within the sample population: Selected patients were screened to avoid current antidepressant use, past diagnosis with a psychotic disorder, serious suicide attempts, or prior psychiatric hospitalization. However, enrolled patients required a score of at least 17 on the GRID-Hamilton depression rating scale (GRID-HAMD), the scale used to evaluate outcomes in this study at weeks 1 and 4 post-treatment with psilocybin. A total of 27 patients were selected and randomized into an immediate-treatment group (weeks 1-4, n = 14) and delayed-treatment group (weeks 5-8, n = 12), which served as a waiting list control condition that later received PAT as well. At baseline, the mean GRID-HAMD score was 22.8 with SD 3.9. Patients receiving immediate treatment showed significant reductions at weeks 1 and 4, with mean scores returning at 8.0

(SD 7.1) during week 1 and 8.5 (SD 5.7) at week 4. Overall, 17 patients demonstrated reductions in GRID-HAMD scores of at least 50%, 14 patients went into remission, and 3 patients dropped out before completing the intervention. Although preliminary, the effect sizes seen with psilocybin in this trial are several times larger than that seen in psychotherapy or antidepressant monotherapy[31-33].

The efficacy of psilocybin seen in depression studies likely offers benefits in a trauma-centered approach, due to the widespread comorbidity of trauma with depressive disorders. The role of psilocybin continues to expand outside its FDA designation for treatment-resistant depression. Khan *et al*[34] reported on an open-label study that provided psilocybin-assisted therapy in traumatized AIDS survivors. The authors noted reductions in PTSD symptoms, attachment anxiety, and demoralization. The intent underlying psychedelic use appears to be important. One survey demonstrated that therapeutic intent behind past psychedelic use in patients with history of child maltreatment showed significant reductions in complex trauma symptoms and internalized shame[35]. This further suggests that psilocybin's benefits extend beyond depression and into trauma-related pathologies. Though outside the scope of the present article, psilocybin is being explored across several domains including substance use disorders, neurodegenerative diseases such as Alzheimer's disease[36].

Adverse reactions

In the psilocybin and escitalopram study, the escitalopram group had a higher prevalence of anxiety, dry mouth, sexual dysfunction, and reduced emotional responsiveness. Due to these side effects, four patients self-discontinued the medication and one patient modified regimen to half a daily dose. No patients in the psilocybin group requested dose adjustment or discontinuation[7]. In the trial by Davis *et al*[31], participants reported mild-to-moderate headache, as well as difficult emotions during in-session time only. No serious adverse events were reported or observed[31].

MDMA

In 2021, Mitchell *et al*[16] reported data from a double-blind, phase 3 clinical trial found that 67% of participants receiving MDMA-assisted psychotherapy ceased to meet PTSD criteria after 2 mo[16]. The MDMA-treated group (n = 46) showed significant decreases on clinician-administered PTSD Scale for DSM-5 (CAPS-V) compared to inactive placebo with therapy (n = 44). Participants attended three experimental sessions, spaced four weeks apart. The first session started with 80 mg MDMA and the option for a supplemental half-dose of 40 mg, 1.5-2.5 h later. For the next two sessions, the initial dose was increased to 120 mg with supplemental half-dose of 60 mg. No tolerability issues led to participants being withheld the supplemental doses.

MDMA-assisted therapy led to increases in posttraumatic growth, encompassing increased positivity towards self-perception, relationships, or philosophy of life[37]. Scores from 60 participants, pooled from three phase 2 clinical studies meeting PTSD criteria, were assigned to treatment with 75-125 mg MDMA (n = 45) or active control (0-40 mg MDMA, n = 15). The MDMA group had significantly improved scores on the posttraumatic growth inventory and greater reduction in PTSD symptom severity at 12 mo, and 67% of participants no longer met criteria for PTSD. MDMA may promote adaptive stress responses in PTSD that lead to the downstream benefits seen in recent research, such as reduced ratings of PTSD symptom severity by clinicians[38,39].

MDMA has also been studied in the setting of couples therapy, in which one partner has a current diagnosis of PTSD. One study included 6 romantic dyads, in which both partners received MDMA followed by couples' cognitive behavioral therapy. This led to improved happiness and significant reductions across PTSD symptoms, as unanimously rated by patient, partner, and clinician[40]. Further analysis of this study found enduring improvements in post-traumatic growth, social intimacy, and relational support at 6-mo follow up[41].

These benefits extend to common comorbidities seen in PTSD such as depression[42], substance use [43] and sleep disorders[44], with improvements in Pittsburgh sleep quality index scores that remained significant at one-year follow up. MDMA also shows promise in various other psychopathologies including eating disorders[45] and end of life anxiety associated with life-threatening illness[46], in which patients reported increased ability to cope as they faced illness and existential fears, as well as overall improved quality of life. See Table 1 for a summary of relevant articles discussed in the above psilocybin and MDMA sections.

Adverse reactions

Mitchell *et al*[16] concluded that MDMA was safe and well-tolerated and note that the treatment did not induce abuse potential, suicidality, or QT prolongation[16]. Other studies show that risk factors for developing hyperthermia may include adolescent age and increased alcohol consumption[47-49]. Hyperthermia and rhabdomyolysis are likely context-dependent, occurring at lower frequency when used with therapeutic intent rather than recreational use in the setting of other risk factors[47,50]. Likewise, the "come downs" previously associated following MDMA use may be due to research confounds related to environment and drug sourcing, as clinically administered MDMA has noticeably

Table 1 Relevant articles to the discussion with the corresponding treatment investigated

Ref.	Publication year	Treatment	Psychiatric diagnosis
Carhart-Harris *et al*[7]	2021	Psilocybin	Depression
Murphy *et al*[30]	2021	Psilocybin	Depression
Davis *et al*[31]	2021	Psilocybin	Depression
Khan *et al*[34]	2022	Psilocybin	Trauma-related disorders in AIDS patients
Healy *et al*[35]	2021	Psilocybin	Complex Trauma
Kozlowska *et al*[36]	2022	Psilocybin	Neurodegenerative disorders
Mitchell *et al*[16]	2021	MDMA	PTSD
Gorman *et al*[37]	2020	MDMA	PTSD
Hoskins *et al*[38]	2021	MDMA	PTSD
Arluk *et al*[39]	2022	MDMA	PTSD
Monson *et al*[40]	2020	MDMA	PTSD
Wagner *et al*[41]	2021	MDMA	PTSD
Bird *et al*[42]	2021	MDMA	Depression
Nicholas *et al*[43]	2022	MDMA	Substance use disorders
Ponte *et al*[44]	2021	MDMA	Sleep disorders
Brewerton *et al*[45]	2021	MDMA	Eating disorders
Barone *et al*[46]	2022	MDMA	End-of-life anxiety associated with life-threatening illness

AIDS: Acquired immunodeficiency syndrome; MDMA: 3,4-methylenedioxymethamphetamine; PTSD: Post-traumatic stress disorder.

lacked this side effect[51]. Other reports in the literature include hepatotoxicity that improved with vitamin E[52], and a case of spinal cord injury suspected to be due to the serotonin surge induced by MDMA, as the vasoconstrictive properties of serotonin may have induced ischemia[53].

FUTURE DIRECTIONS

Dual therapy

As the evidence for each treatment builds independently, the future may include the integration of both treatments in sequence. In this scenario, MDMA would likely be used first as it has a larger influence on building therapeutic alliance. The augmented therapeutic alliance would allow for a potentially improved psilocybin experience upon switching at next session, aligning with previously discussed research that strong therapeutic alliances are associated with greater mystical experiences and emotional breakthroughs. Treatment with MDMA has been associated with persistent depressive symptoms, and the antidepressant effects of psilocybin may alleviate this following administration[42]. In a model described by Oehen and Gasser[54], MDMA tended to be used in the first phase to build the therapeutic alliance and increase the patient's openness to change, leading to enhanced resilience and lowered stress levels. Once further changes were noticed, such as improved self-regulation, less negative self-perception, and increased tolerance to trauma exposure, LSD was introduced to assist psychotherapy. The deepening of the therapeutic process led to improvement per clinical judgment, without adverse events.

Standardization

Although variation in research methodology is needed to enrich the literature pool, standardization in several aspects may allow for more informed comparisons between treatment modalities. Symptom rating scales for depression (*i.e*, QIDS-SR, GRID-HAMD) and PTSD (*i.e*, CAPS-IV, CAPS-V) varied, with some studies using subjective reports of PTSD diagnostic criteria. Similarly, the therapy modalities that accompanied psychedelic administration were diverse, including uniquely developed forms of therapy as in the accept-connect-embody manualized therapy developed in a psilocybin trial[7,30], supportive therapy[31], and couples' cognitive behavioral therapy[40]. The future may look more like the manualized MDMA-assisted therapy provided through public benefit corporation Multidisciplinary Association for Psychedelic Studies (MAPS). MAPS also has an ethics code, a vital addition to future

protocols as patients are placed in a state of increased suggestibility and affective instability during and after the treatment[55]. This critical period requires a trauma-informed approach to care, with support for transgender and gender diverse patients[56]. Lastly, the method of eliciting adverse drug reactions may benefit from standardization. Studies varied in terms of asking open-ended questions, prompting for specific symptoms, and documenting clinical observations. It is comforting that current studies have not shown any serious adverse events, and future studies may benefit by drawing upon a standardized set of common symptoms.

Wearables

Wearable technology has previously demonstrated efficacy as a bridge between patients and providers in mental health, such as in MDD, dementia, schizophrenia[57-59]. Wearables are likewise being used in non-psychiatric contexts, including medical monitoring in oncology and gastroenterology[60,61]. It follows that wearables may have clinical utility in monitoring patient symptoms during and after PAT. Daily functioning, including wearable-derived sleep and activity data, is incorporated in a protocol examining the effects of microdosed psychedelics and may be a useful metric to track long term changes following psychedelic treatment[62].

CONCLUSION

The literature on PAT using psilocybin or MDMA is strongly supportive across psychiatric conditions, especially trauma and related comorbidities. Both treatments seem to have benefits beyond the FDA breakthrough designations of treatment-resistant depression for psilocybin and PTSD for MDMA. As adjuncts to psychotherapy, psilocybin and MDMA show a pattern of rapid and sustained symptom relief. Future studies may consider the advantages of a standardized approach to symptom rating scales, therapy styles, and assessment of adverse drug reactions. Wearables may also offer additional metrics to examine the long-term trends in activity and sleep. As clinical trials continue to show positive results, providers and patients become closer to seeing the effects translate to the clinic and the community.

FOOTNOTES

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Effect of exercise prescription teaching on exercise quality and mental health status of college students

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Abstract

BACKGROUND

The teaching mode of fitness exercise prescriptions for college students in physical education conforms to the scientific principles and rules of fitness, which can adapt to the characteristics of students' individual physiological functions and stimulate their interest in learning.

AIM

To analyze the effect of prescribed exercise teaching on the sports quality and mental health of college students.

METHODS

The participants of the study were 240 students in our class of 2021, of which 142 were men and 98 were women. The 240 students were randomly divided into an experimental group using the exercise prescription teaching model and a control group using the conventional teaching model. The experimental and control groups were divided into four classes of 30 students each. The teaching activities of the two teaching mode groups were strictly controlled, and the same tests were used before and after the experiment to test the subjects' exercise quality (including standing long jump, 50 m race, 800 m race, sit-ups, sit-and-reach), physical form (including height, weight, Ketorolai index), cardiopulmonary function (including heart rate, blood pressure, spirometry, 12-min running distance, maximum oxygen intake) and mental health (SCL-90, including somatization, obsessive-compulsive, interpersonal, depression, anxiety, hostility, phobia, paranoia, psychotic symptoms) to understand the effects of the exercise prescription teaching mode on students' physical and mental health status.

RESULTS

There were differences in the exercise scores of standing long jump, 50 m, 800 m/1000 m running, sit-ups, and sit-and-reach in the experimental group after the experiment compared with those before the experiment, and the above indices of

the experimental group were different from those of the control group after the experiment ($P < 0.05$). There were differences in body weight and Ketorolai index in the experimental group after the experiment compared to those before the experiment, and the indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$). After the experiment, there were differences in spirometry, 12-min running distance, and maximum oxygen intake in the experimental group compared to those before the experiment, and the indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$). After the experiment, the indicators of somatization, interpersonal sensitivity, depression, anxiety, and hostility in the experimental group were different from those in the pre-experimental group, and the indexes of the experimental group were also different from those of the control group after the experiment ($P < 0.05$).

CONCLUSION

Exercise prescription teaching can mobilize college students' consciousness, enthusiasm, and initiative; expand personalities; enhance physical fitness and improve their mental health more than the conventional fitness exercise prescription teaching method.

Key Words: Exercise prescription teaching; College students; Exercise quality; Mental health status

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Core Tip: In order to better create a positive and optimistic outlook on life for college students and increase their interest in physical exercise, it is necessary to apply the physical health prescription course in the process of school physical education teaching. By using sports prescription teaching, teachers develop targeted teaching contents and methods in the teaching class according to the physical quality and health status of students, combine the teaching materials with students' self-learning, self-exercise, self-control, self-regulation and self-evaluation, give full play to students' main role, mobilize students' subjective initiative, realize the transformation from exam-oriented education to quality education, and promote students' all-round development. In view of the continuous decline in the physical and mental health of college students, based on the perspective of special teaching of physical education in colleges and universities, this study starts with the diagnosis of students' physique, provides students with personalized sports prescription teaching experiments with the main purpose of promoting physique, and provides scientific basis for improving students' current physical and mental health, guiding students to conduct scientific and reasonable physical exercise, and improving the effectiveness of school physical education.

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INTRODUCTION

Higher general education institutions are the cradles of training qualified personnel of comprehensive quality[1]. College students, as practitioners of China's social, economic development and socialist core values, play the role of the backbone in the future development of society. Ensuring the mental health of college students is increasingly becoming a real problem in the development of China[2,3]. In recent years, problems concerning the physical and mental health of college students have also become the focus of attention, and the results of a large number of surveys and studies[4-6] have shown that the physical conditions, psychological and mental health problems of contemporary college students are more prominent than previously. Therefore, there is an urgent need to find practical and effective measures to strengthen the mental health education and physical exercise of college students, and to strive to improve the physical and mental health of college students.

To create a more positive and optimistic outlook on the lives of college students, as well as to increase their interest in physical exercise, it is necessary to apply physical health prescription courses in the process of physical education in schools[7]. In the traditional process of teaching physical education in institutions, the lack of attention given to exercise health by teachers and students has left many college students facing health problems. Exercise prescription teaching is a highly targeted teaching content and method developed by teachers according to students' physical fitness and health status. It combines teaching according to the material with students' self-learning, self-practice, self-control, self-regulation,

and self-assessment, which can realize the transition from examination-based education to quality education and promote students' overall development by providing full attention to the main role of students and mobilizing their subjective initiative[8-10]. Currently, colleges and universities are making unremitting efforts to continuously "enhance students' physical fitness" and implement "lifelong sports." The physical education mode of self-management and self-development for college students by developing different exercise and fitness prescriptions is beneficial to the physical and mental development of college students.

In response to the trend of continuous decline in the physical and mental health of college students, based on the perspective of college physical education special teaching, this study conducted physical fitness tests on students before the experiment, analyzed the students' various test results, corresponding indices, and provided students with personalized exercise prescription teaching experiments with the main purpose of promoting physical fitness for students' deficiencies in endurance, speed, and strength. It is expected to provide a scientific basis for improving students' current physical and mental health, guide students toward scientific and reasonable fitness, and improve the effectiveness of school physical education.

MATERIALS AND METHODS

Study population

In this study, 240 students from our school class of 2021 were randomly selected (142 men and 98 women), and all participants had no contraindications to sports after taking their medical history and physical examination. The 240 students were randomly divided into an experimental group using the exercise prescription teaching model and a control group using the conventional teaching model. In the experimental group, there were four classes of 30 students each with a total of 120 students, including 69 men and 51 women, aged 18-21 years, with a mean of (19.21 ± 0.61) years. In the control group, there were four classes of 30 students each with a total of 120 students, including 73 men and 47 women, aged 18-20 with a mean of (19.16 ± 0.39) years. The differences in baseline information such as sex, age, height, and weight between the two groups of students were not statistically significant ($P > 0.05$) and were comparable. The study was approved by our ethics committee and all participants signed an informed consent form.

Literature method

We reviewed many articles and textbooks related to exercise prescription teaching as well as teaching curriculum reform and collected the results of domestic and international research on exercise prescription in recent years through Internet searches and other methods for an in-depth understanding of the current state of research and cutting-edge development. Simultaneously, relevant literature was organized and analyzed to provide more informative theoretical data and case support for the study.

Questionnaire method

Questionnaire content: A questionnaire was developed for the implementation of exercise prescription teaching, and the students were divided into experimental and control groups; the results were analyzed and compared in depth. The survey effectively reflected students' opinions on physical education classes, which laid the foundation for the future development of exercise prescription teaching. The survey reflected students' exercise attitudes, learning habits, interests, and other aspects. This way, a scientific exercise prescription curriculum could be effectively developed.

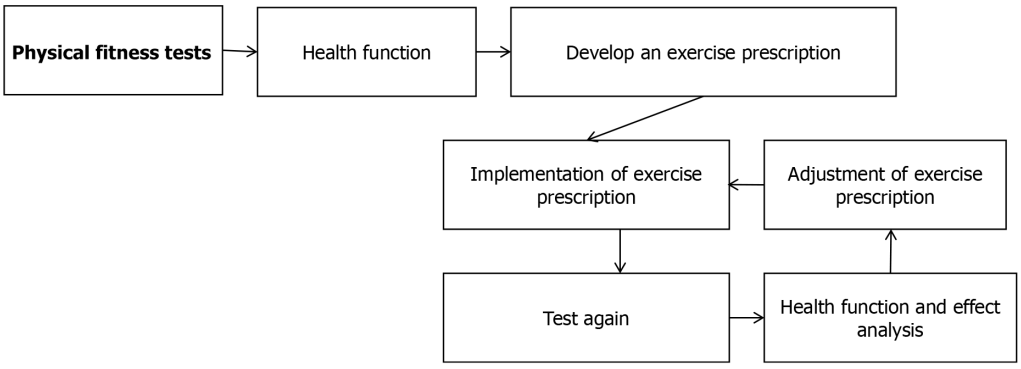
Distribution and recovery of questionnaires: Students in the experimental and control groups participated in a questionnaire survey (Table 1).

Experimental content

Exercise prescription teaching is a highly targeted teaching method developed by the teacher according to the physical fitness and health status of students in the teaching class. It was a method in which the teacher combined the teaching of students according to their abilities with self-learning, self-practice, self-control, self-regulation, and self-assessment. By providing full attention to the main role of students and mobilizing their initiative to achieve the transition from examination-based to quality education, we promoted the overall development of students. The experimental group and the control group were both taught by the same physical education teacher. The experimental group used "exercise prescription" as the basic teaching procedure, the implementation process was cyclic and repetitive (Figure 1). A physical fitness test was conducted to evaluate the exercise ability of students and will be used as the basic basis for exercise prescription control. Teachers analyzed the students' physical fitness according to comprehensive scoring levels in the National Student Physical Fitness Standards and assessed their health functions. Corresponding to the weaknesses of the students in the experimental group, relevant exercise prescriptions (development of speed quality exercise prescription, development of muscle strength exercise prescription, development of endurance exercise prescription, improvement

Table 1 Statistics on the distribution and return of questionnaires

Number of actual issue	Number of recoveries	Recovery rate (%)	Effective number	Effective rate (%)
240	240	100%	240	100%



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Figure 1 Diagram of the implementation process of exercise prescription in the experimental group.

of physical function exercise prescription, *etc.*) were designed to develop appropriate exercise content, exercise load, intensity, frequency, and duration; each exercise prescription determines the upper and lower limits of effective physical exercise for the students[11,12]. The experimental group participated in one physical education class (two class periods) and two extracurricular physical activities every week and exercised according to the formulated exercise prescription. Teachers conducted physical fitness tests every four weeks and adjusted the exercise program according to the actual situation of students to ensure the scientific nature of students' physical exercise. The control group was taught according to the normal physical education syllabus (including formation and assembly, teachers and students greeting each other, teacher briefly introducing the teaching content and requirements, yoga to warm up, and starting exercise), with one physical education class (two class periods) per week and two extracurricular physical activities conducted by the students themselves.

Teaching plan

The exercise prescription intervention lasted for 16 wk, as shown in Table 2.

Observation index

Motor quality: The test items included the standing long jump, 50-meter run, 800-meter run, sit-up, and sit-and-reach. The tests were conducted and scored on a standard athletic field using standard sports equipment. The test content and test methods were tested in accordance with the requirements of the "Student Physical Fitness Standards (pilot program)" published by the People's Education Publishing House. Measurements were taken before and after the experiment, and specific values were recorded.

Body shape: Included height, weight, and Ketorai index. The equipment used for height and weight measurement was the XTC series of student body mass measurement instruments sold by Dandong Tiankang Sporting Goods Co. Measurements were taken before and after the experiment, and specific values were recorded.

Cardiopulmonary function: Heart rate was measured directly by an electronic meter using the manual pulse measurement method; blood pressure was measured using a mercury sphygmomanometer; spirometry was measured using a Tiankang XTC series student physical measurement spirometer, and a total of three measurements were taken at 15 s interval each time, and the maximum value was taken as spirometry. Maximal oxygen uptake: Extrapolation was done by 12 min running distance performance, and a 12 min running distance was measured on the track of a 400 m standard athletic field. After measuring the 12-min running distance, the maximum oxygen uptake per kilogram of body weight was determined using an extrapolation table developed by the Japan Sports Science Center. Measurements were taken before and after the experiment, and specific values were recorded.

Mental health: A name-based questionnaire was used to assess the mental health status of students using the SCL-90, a self-assessment scale for mental health and psychiatric conditions in China. The scale has 90 items, and the severity level is classified according to the weight of each item (Table 3). This scale consists of 10 main factors: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, fear, paranoia, psychoticism, and others. The high-weighting factor also

Table 2 Specific contents of the exercise prescription teaching program in the experimental group

Teaching content	Number of exercise sets	Exercise intensity	Exercise time	Heart rate (beats/min)	
				Average	Highest
In-class exercise					
1 Preparatory activities: Jogging and marching unarmed exercise.		30-40	15	100	130
2 Normal teaching content.		50-75	40	140	160
3 Exercise content: Focus on the development of strength, agility, speed and endurance qualities.		60-80	30	150	180
(1) Fast moving exercises.	2-3				
(2) Chest, back, abdominal, arm muscles and other parts of the comprehensive apparatus strength exercises.	6-8				
(3) Single and double leg jumping steps.	3-4				
(4) Standing jump, multi-level jump.	3-4				
(5) Various development of aerobic endurance quality exercise.	4-5				
4 Relaxation and finishing exercises.	2-3	20-40	5	100	120
Extracurricular sports					
1 Preparatory activities: Jogging and marching unarmed exercise.		30-40	10	100	120
2 Exercise content: Focus on the development of strength, agility, speed and endurance qualities.		60-80	15	150	180
(1) Fast moving exercises.	3-4				
(2) Holding light equipment strength exercises.	8-10				
(3) Single and double leg jumping steps.	3-4				
(4) Standing jump, multi-level jump.	3-4				
(5) Various development of aerobic endurance quality exercise.	4-5				
3 Relaxation and finishing exercises.	2-3	30-40	5	100	120

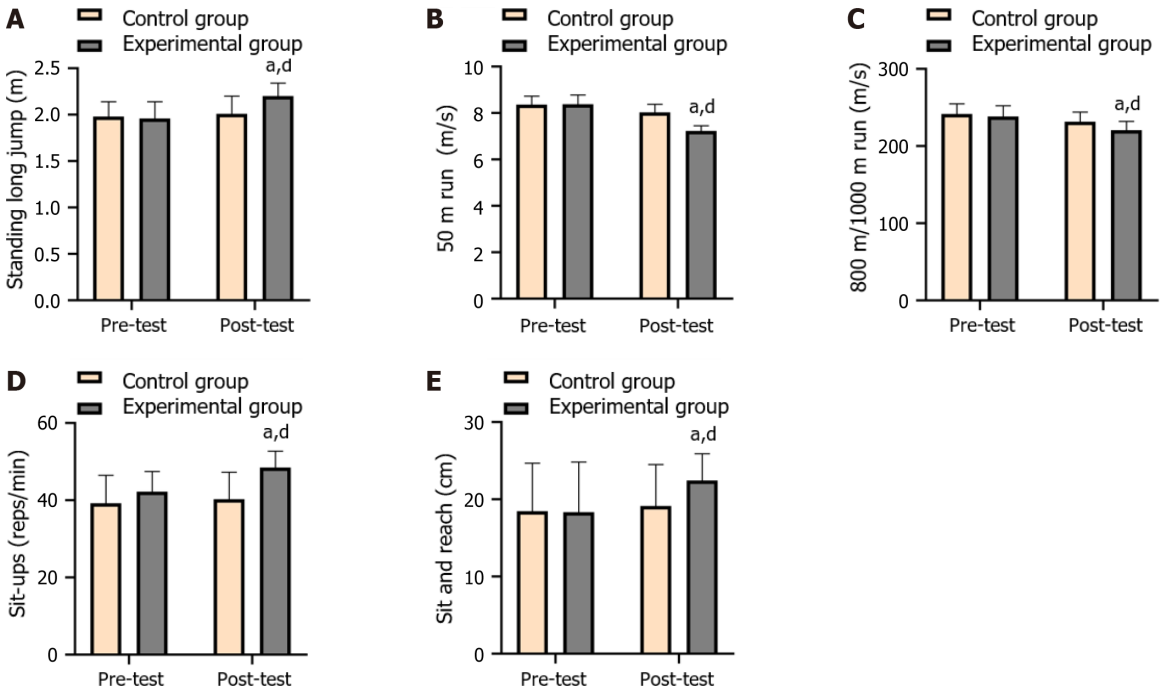
Table 3 Classification of SCL-90 severity levels

Serial number	Grade	Symptom
1	No	Self-perceived absence of symptoms
2	Mild	Conscious presence of the symptom, but no real effect on the subject
3	Moderate	Conscious presence of the symptom, with some effect on the subject
4	Fairly severe	The symptom is often perceived and has a significant impact on the subject
5	Severe	The frequency and intensity of symptoms are very severe

laterally reflects the presence of mental health problems. Measurements were taken before and after the experiment, and specific values were recorded.

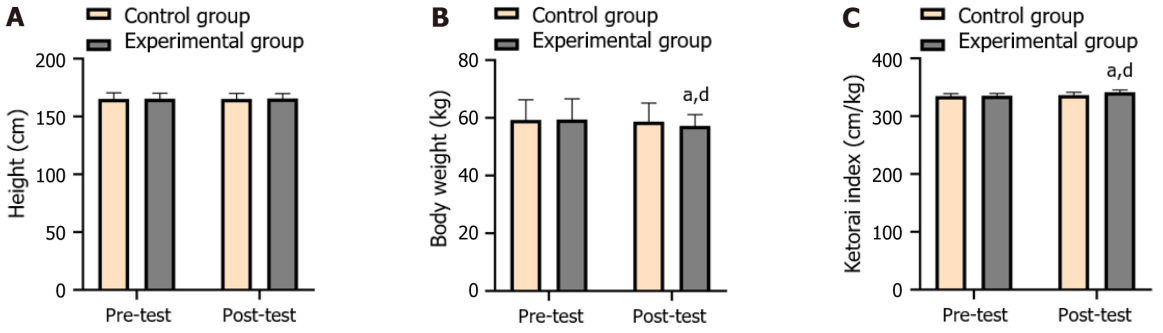
Statistical analysis

The relevant data obtained from the survey and test before and after the experiment were analyzed using SPSS 20.0, and a *t*-test was conducted to verify whether there were differences between the experimental and control groups. Therefore, the experimental results were quantified and the objectivity and feasibility of the study were ensured.



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Figure 2 Comparison of exercise quality between the two groups before and after the experiment. A: Standing long jump test (m); B: 50 m run test (m/s); C: 800 m/1000 m run test (m/s); D: Sit-up test (reps/min); E: Sit and reach test (cm). $^{a}P < 0.05$ *vs* the same group before test. $^{d}P < 0.05$ *vs* the control group after test.



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Figure 3 Comparison of body morphology between the two groups before and after the experiment. A: Height (cm); B: Weight (kg); C: Ketorai index (cm/kg). $^{a}P < 0.05$ *vs* the same group before teaching. $^{d}P < 0.05$ *vs* the control group after teaching.

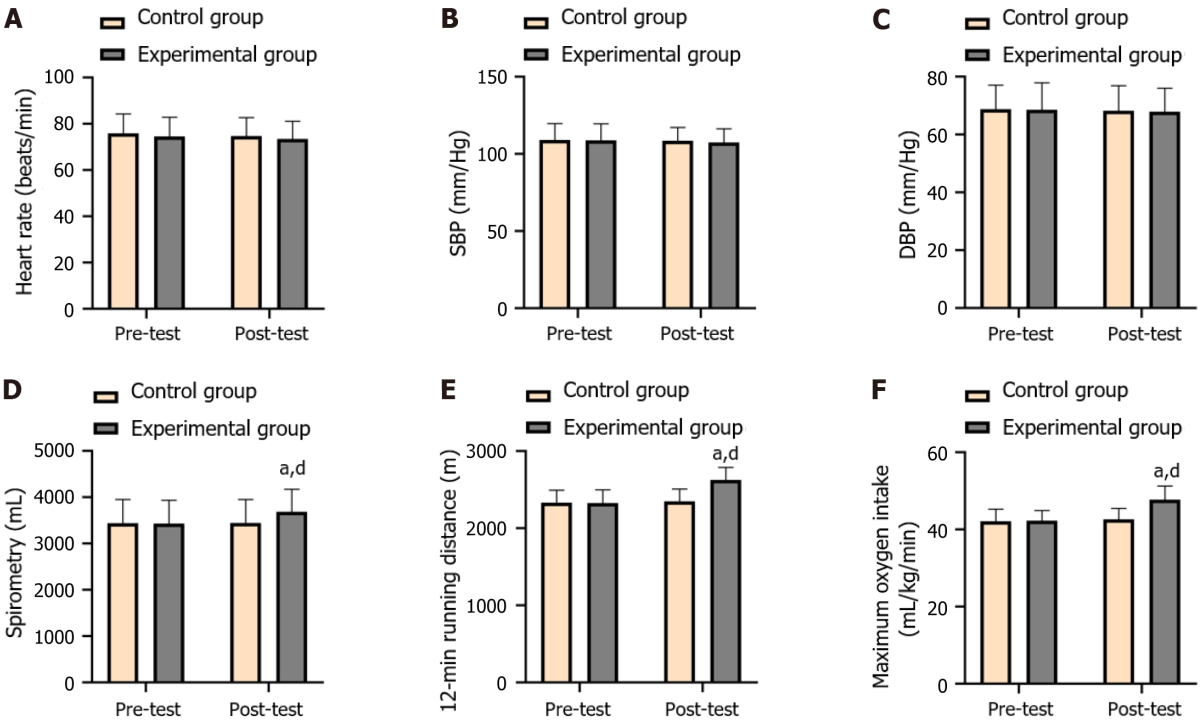
RESULTS

Comparison of exercise quality between the two groups before and after the experiment

The differences between the two groups in the pre-experimental exercise test scores for standing long jump, 50 m, 800 m/1000 m running, sit-ups, and sit-and-reach were not significant ($P > 0.05$). After the experiment, there were differences in the exercise scores of standing long jump, 50 m, 800 m/1000 m running, sit-ups, and sit-and-reach in the experimental group compared with those before the experiment, and the indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$) (Figure 2).

Comparison of body morphology between the two groups before and after the experiment

The differences in height, weight, and Ketolai index before the experiment were not significant between the two groups ($P > 0.05$). There were differences in body weight and Ketolai index in the experimental group after the experiment compared with the pre-experimental group. The above indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$), and there were no significant differences in height between the two groups before and after the experiment ($P > 0.05$) (Figure 3).



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Figure 4 Comparison of cardiopulmonary function between the two groups before and after the experiment. A: Heart rate (beats/min); B: Systolic blood pressure (mm/Hg); C: Diastolic blood pressure (mm/Hg); D: Spirometry (mL); E: 12-min running distance (m); F: Maximum oxygen intake (mL/kg/min). [a]*P* < 0.05 *vs* the same group before teaching. [d]*P* < 0.05 *vs* the control group after teaching. SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Comparison of cardiopulmonary function between the two groups before and after the experiment

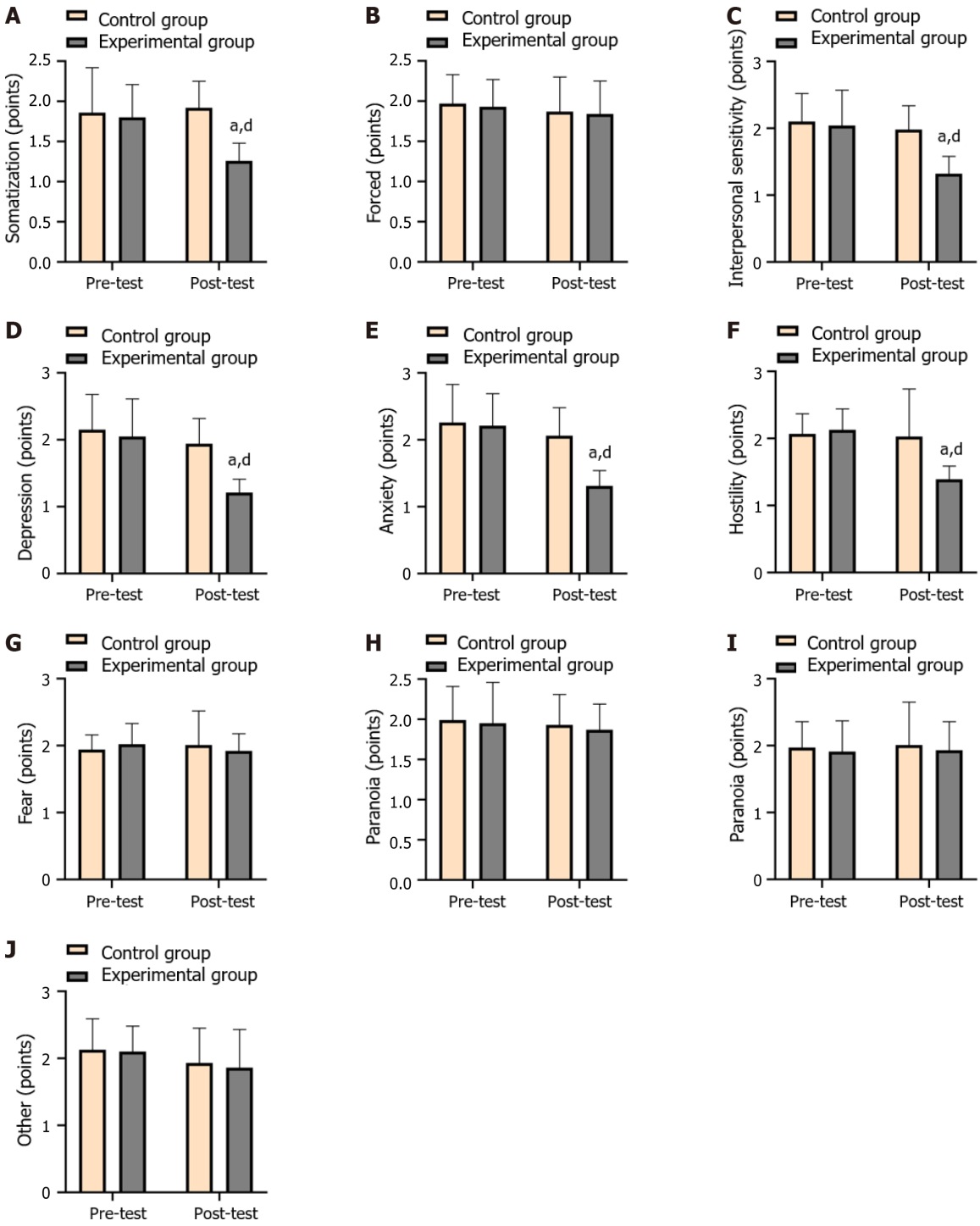
The differences between the two groups in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), spirometry, 12-min running distance, and maximum oxygen intake before the experiment were not significant ($P > 0.05$). There were differences in the post-experimental spirometry, 12-min running distance, and maximum oxygen uptake in the experimental group compared with those before the experiment; the above indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$), and there were no significant changes in heart rate, SBP, and DBP levels before and after the experiment in both groups ($P > 0.05$) (Figure 4).

Comparison of the mental health status of the two groups before and after the experiment

Differences in the indicators of somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, and paranoia were not significant between the two groups before the experiment ($P > 0.05$). Post-experimental somatization, interpersonal sensitivity, depression, anxiety, hostility, and other indicators in the experimental group differed from the pre-experimental comparison. These indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$). The post-experimental compulsion, fear, paranoia, psychoticism, and other index scores of the experimental group did not differ significantly from the pre-experimental scores, nor did they differ significantly from those of the control group ($P > 0.05$). No significant changes were seen in the index scores of the control group before and after the experiment ($P > 0.05$) (Figure 5).

DISCUSSION

In recent years, problems regarding the physical and mental health of college students have become a focus of attention, and the results of a large number of surveys and studies have shown that the physical conditions, psychological and mental problems of contemporary college students are very prominent [13,14]. The exercise prescription teaching mode interrupted the teaching material system of teaching competitive sports technology and established a fitness-centered fitness teaching system that realized the consistency of teaching purpose, content, and form and made the enhancement of physical fitness come into practice[15-17]. This study explored interventions for college students' mental health through sports and the use of exercise prescriptions to find new ways to improve college students' mental health.



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Figure 5 Comparison of the mental health status of the two groups before and after the experiment. A: Scores of somatization (points); B: Scores of forced (points); C: Scores of interpersonal sensitivity (points); D: Scores of depression (points); E: Scores of anxiety (points); F: Scores of hostility (points); G: Scores of fear (points); H: Scores of paranoia (points); I: Scores of psychotic (points); J: Scores of other (points). $^{a}P < 0.05$ *vs* the same group before teaching. $^{d}P < 0.05$ *vs* the control group after teaching.

Effect of exercise prescription teaching on students' motor quality

As can be seen from Figure 2, the results of motor quality tests after the experiment for students in the experimental group showed significant changes in motor ability such as a 50 m run, 800 m/1000 m run, standing long jump, sit up, and sit-and-reach show significant changes, indicating that the students' speed, endurance, spring, and upper body strength have been greatly improved. The reason for this may be that the exercise prescription instruction is well arranged and has a good effect on improving all aspects of students' abilities The above suggests that college students should pay attention to strength training, especially the strength training of lower limbs and shoulder belt muscles[18,19].

Effect of exercise prescription teaching on students' body morphology

After the exercise prescription teaching mode exercise, body morphological indices such as height, weight, and Ketorai index before and after the experiment in the control group were not significantly different, whereas there was little change in height before and after the experiment in the experimental group, which was related to the basic stability of bone development in college students. The weight and Ketorolai index of the experimental group differed significantly after the experiment compared with those before the experiment, which may be related to an increase in physical exercise and energy consumption. Slight weight loss is a good adaptation to exercise, and a more significant weight loss may be related to the physical condition of the subject and the content of the exercise received; however, these are all normal conditions[20].

Effect of exercise prescription teaching on students' cardiorespiratory function

From the changes of cardiopulmonary function assessment indexes before and after the experiment. There was no significant difference between the cardiopulmonary function indexes of the experimental group and the control group before the experiment. After the experiment, the vital capacity, 12-min running distance, maximum oxygen intake, step index, and other indices of the experimental group were different from those before the experiment and from those of the control group. The changes in the indexes of students' cardiorespiratory fitness indicate the enhancement of physical fitness and the improvement of exercise capacity, and that the physical exercise of the exercise prescription teaching model has greatly improved students' physical quality and mastery of athletic skills[21,22].

Effect of exercise prescription teaching on students' mental health status

The average score of the SCL-90 scale in the experimental group showed that after 16 wk of exercise prescription teaching, the scores of all factors in the experimental group were decreased, and the scores of interpersonal relationship, anxiety, and depression factors were significantly decreased, and there were very significant differences when compared with those before the experiment. This shows that the implementation of a fitness exercise prescription affected the psychological health of the experimenter. The university stage is a period of gradual maturation of students' psychological processes and complex psychological changes. In a good classroom atmosphere, students experience the pleasure of living with teachers and other students through the medium of cognition and emotion. The elimination of negative emotions caused by the social environment through exercise can have good short- and long-term benefits on the psychological quality of students[23,24].

CONCLUSION

Students can master practical methods to strengthen their bodies and be better prepared for "lifelong sports" activities. Through this study, we found that the application of an exercise prescription teaching model in tertiary institutions has some limitations, such as venues, instruments, equipment, resulting in the limited tests and exercises that can be completed. Therefore, it is impossible to develop comprehensive, effective, and targeted exercise prescriptions. In a follow-up study, we may consider combining social professional outreach training with college sports to provide the necessary conditions for a comprehensive design of exercise prescription training.

ARTICLE HIGHLIGHTS

Research background

The teaching mode of fitness exercise prescriptions for college students in physical education conforms to the scientific principles and rules of fitness, which can adapt to the characteristics of students' individual physiological functions and stimulate their interest in learning.

Research motivation

The physical, psychological, and mental health problems of contemporary college students are more prominent than ever. Therefore, there is an urgent need to find practical and effective measures to strengthen mental health education and physical exercise for college students, and strive to improve their physical and mental health. In order to have a more positive and optimistic view of the lives of college students and increase their interest in physical exercise, it is necessary to apply physical fitness prescription courses in school physical education teaching. In the traditional physical education teaching process in colleges and universities, teachers and students pay insufficient attention to sports health, resulting in many college students facing health problems.

Research objectives

Currently, the main research is to assess the physical fitness and mental health of college students, and this field will continue in the future.

Research methods

Total 240 students were randomly divided into an experimental group and a control group. The experimental group used exercise prescription teaching mode, while the control group used traditional teaching mode. The experimental group and the control group were divided into four classes with 30 students in each class. Strictly control the teaching activities of the two teaching mode groups, and use the same tests before and after the experiment to test the exercise quality, body shape of the subjects, Cardiopulmonary function and mental health to understand the impact of sports management teaching models on students' physical and mental health.

Research results

In response to the trend of continuous decline in the physical and mental health of college students, based on the perspective of college physical education special teaching, this study conducted physical fitness tests on students before the experiment, analyzed the students' various test results, corresponding indices, and provided students with personalized exercise prescription teaching experiments with the main purpose of promoting physical fitness for students' deficiencies in endurance, speed, and strength. It is expected to provide a scientific basis for improving students' current physical and mental health, guide students toward scientific and reasonable fitness, and improve the effectiveness of school physical education.

Research conclusions

Sports prescription teaching can mobilize college students' consciousness, enthusiasm, and initiative, and improve their mental health level.

Research perspectives

Through this study, we found that the application of an exercise prescription teaching model in tertiary institutions has some limitations, such as venues, instruments, equipment, resulting in the limited tests and exercises that can be completed. Therefore, it is impossible to develop comprehensive, effective, and targeted exercise prescriptions. In a follow-up study, we may consider combining social professional outreach training with college sports to provide the necessary conditions for a comprehensive design of exercise prescription training.

FOOTNOTES

Author contributions: Zhong XL conceptualized and designed the study, and collected and compiled the data; Sheng DL provided administrative support; Chen TZ provided the research materials and patients; Zhang ZW and Chen TZ analyzed and interpreted the data; and all authors wrote and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Functional near-infrared spectroscopy in elderly patients with four types of dementia

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Abstract

BACKGROUND

Functional near-infrared spectroscopy (fNIRS) is commonly used to study human brain function by measuring the hemodynamic signals originating from cortical activation and provides a new noninvasive detection method for identifying dementia.

AIM

To investigate the fNIRS imaging technique and its clinical application in differential diagnosis of subtype dementias including frontotemporal lobe dementia, Lewy body dementia, Parkinson's disease dementia (PDD) and Alzheimer's disease (AD).

METHODS

Four patients with different types of dementia were examined with fNIRS during two tasks and a resting state. We adopted the verbal fluency task, working memory task and resting state task. Each patient was compared on the same task. We conducted and analyzed the fNIRS data using a general linear model and Pearson's correlation analysis.

RESULTS

Compared with other types of dementias, fNIRS showed the left frontotemporal and prefrontal lobes to be poorly activated during the verbal fluency task in frontotemporal dementia. In Lewy body dementia, severe asymmetry of prefrontal lobes appeared during both verbal fluency and working memory tasks, and the patient had low functional connectivity during a resting state. In PDD, the patient's prefrontal cortex showed lower excitability than the temporal lobe during the verbal fluency task, while the prefrontal cortex showed higher

excitability during the working memory task. The patient with AD showed poor prefrontal and temporal activation during the working memory task, and more activation of frontopolar instead of the dorsolateral prefrontal cortex.

CONCLUSION
Different hemodynamic characteristics of four types of dementia (as seen by fNIRS imaging) provides evidence that fNIRS can serve as a potential tool for the diagnosis between dementia subtypes.

Key Words: Functional near-infrared spectroscopy; Frontotemporal lobe dementia; Lewy body dementia; Parkinson's disease dementia; Alzheimer's disease

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Core Tip: Four types of dementia showed different patterns of activation when examined by functional near-infrared spectroscopy (fNIRS) during two tasks and a resting state. The patient with frontotemporal dementia showed the lowest activation during the verbal fluency task and the patient with Alzheimer's disease showed the lowest activation during the working memory task. During the resting state, functional connectivity was poor in the patients with Lewy bodies dementia and Parkinson's disease dementia. fNIRS imaging in dementia patients may be able to differentiate between types of dementia, and may be useful in diagnosis for these patients.

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INTRODUCTION

Dementia is a disease commonly studied in psychiatry and neurology. Clinical diagnosis is based on symptoms and is supplemented by neuropsychological scales and laboratory examinations. Brain imaging technology is an important tool for exploring brain diseases, and has undergone a period of rapid development in the past 20 years. To improve the accuracy of diagnosis between types of dementia, different technologies have been developed, including computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) to examine brain structure, electroencephalography (EEG) to examine electrical physiology[1]. In addition to functional MRI (fMRI), EEG, and event-related potentials, functional near-infrared spectroscopy (fNIRS) to examine functional connectivity between regions has become an important supplement to existing functional imaging technologies[2,3].

fNIRS imaging evaluates human brain activity by measuring the oxygen level in the prefrontal and temporal cortices[4]. While participants perform different tasks, the fNIRS system provides continuous and real-time oxygen change display of oxy-hemoglobin (oxy-Hb) and deoxygenated hemoglobin values[5]. In aspects of specificity and temporal resolution, fNIRS assessment of cognitive function eliminates many shortcomings of fMRI[6]. While PET and MRI studies have generated insights into the pathological changes in brain oxygenation and activity associated with mild cognitive impairment (MCI) and dementia, these methods have some limitations involving the injection of radioactive compounds and motion artifacts[7].

fNIRS imaging systems possess high temporal and spatial resolutions, which are critical to withstand interference (both electromagnetic and from head motion). The temporal resolutions of fNIRS (11 Hz in this study) and EEG are in the order of seconds and milliseconds, respectively. The spatial resolution of fNIRS (3 cm in this study) was higher than that of EEG[8,9]. Because EEG recording is a surface potential change of skull, the accuracy of spatial localization is not high. fNIRS probe acquires the cortical activity directly and has a centimeter level of resolution[10]. fNIRS is used to monitor hemodynamic changes evoked by neural activity by taking advantage of the fact that biological tissues are relatively transparent to near-infrared light 700-1000 nm[11]. Recent studies on fNIRS detection of dementia focused on MCI and Alzheimer's disease (AD)[12,13]. It was shown that resting-state fNIRS recordings from prefrontal regions can provide a potential methodology for detecting MCI and its progression[14]. The sensitivity and specificity increase as the cognitive impairment worsens[15].

Amnestic MCI is more predictive of AD than nonamnestic MCI, and nonamnestic MCI is more predictive of other types of dementia including Lewy bodies dementia (LBD) and frontotemporal dementia (FTD)[16,17]. To measure cortical activation in patients with behavioral variant of the FTD (bvFTD), fNIRS was used while performing the verbal fluency task[18]. The flexible of fNIRS makes the possibility of measurement of the neurology of gait in cognitive dysfunction or dementia during dual-task gait assessment[19]. Similar studies focused on old people with risk of dementia, such as those with subjective memory complaints, were reported to be examined by fNIRS indual-task gait[20].

The use of optical techniques, specifically fNIRS, to study brain hemodynamics and to assess prefrontal cortex's activity of older adults for detection of certain types of seizures and cortical spreading deactivation in cognitive tasks is also important. fNIRS can be useful to investigate the altered prefrontal mechanisms of neurological and neuropsychiatric diseases and discover neuroimaging biomarkers for different neurodegenerative disorders[21-24]. The reliability of fNIRS in estimating global cerebral function was supported by previous studies[25]. fNIRS measurements are reproducible and can be reliable used in single subjects for neuroscientific research and clinical applications[26]. It could be a critical tool to investigate frontal lobe oxygenation in patients with different types of dementia and age-related decline of neurovascular coupling responses[27,29].

In this study, using fNIRS, we examined brain functional patterns in patients with four types of dementia: FTD, LBD, Parkinson's disease dementia (PDD), and AD. Because of neurovascular coupling, different types of dementia may cause different hemodynamic alterations. Here, we report four subjects in which fNIRS was used to examine the brain function of patients with dementia (during two tasks and a resting state).

MATERIALS AND METHODS

fNIRS data acquisition

Patients with FTD, LBD, PDD, and AD signed an informed consent form and underwent routine fNIRS examinations at a brain function testing center in the hospital. A multi-channel continuous-wave fNIRS imaging system (Nirscan, Danyang Huichuang Medical Equipment Co. Ltd, China) was employed to measure signals from the frontal and bilateral temporal cortices as described in our previous study[8]. This light-emitting diode-based fNIRS system contained 24 light sources and 24 detectors. The distance between detectors was 3 cm, as shown in Figure 1. The center detector of the middle probe set row was placed at FPz, according to the 10/20 international system. The sampling rate was 11 Hz and the wavelengths used were 780, 808, and 850 nm.

Verbal fluency task

The verbal fluency task consisted of three steps: (1) Participants repeatedly counted from 1 to 5 for 30 s to obtain the baseline value of cognitive performance; (2) during the task period, participants were instructed to generate as many words as possible, they continuously named different words beginning with a specific letters for 20 s (trials for three letters totaled 60 s); and (3) participants repeated step 1 for 70 s to return to baseline. The task took less than three minutes total. Other matters needing attention were described in previous studies on verbal fluency task of fNIRS[30-33].

Memory task

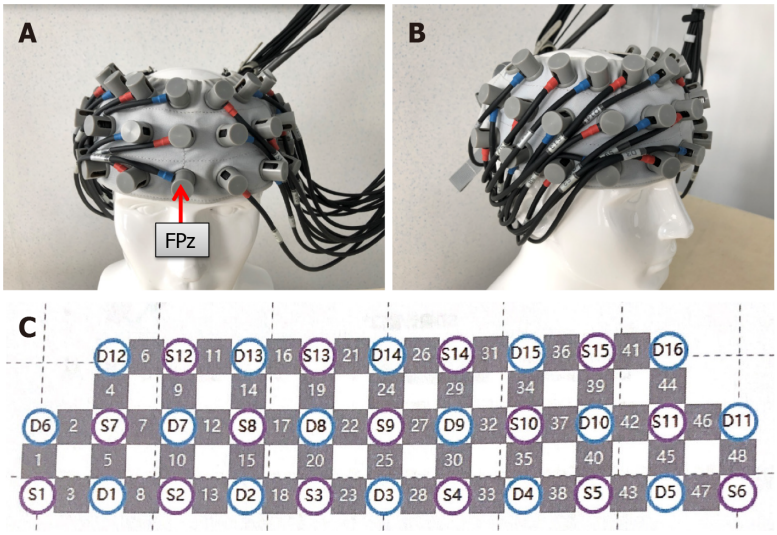
The memory task contained two components on a tablet computer: A working memory search task and a non-working memory search task. In the working memory search task, three graphic icons appeared. Participants were instructed to remember the colors, shapes, and order in which they appeared; subsequently, they were asked to identify the icons in the summary diagram. In the non-working memory search task, participants only needed to select the icons when prompted. The two sets of tasks were alternated and repeated four times. Working memory performance was used to reflect the cognitive function in many studies[34-36].

Resting state

The resting-state signal was recorded continuously for at least 10 min, during which participants were required to sit still and close their eyes without falling asleep. Functional connectivity was calculated on a scale from 0 to 1, where 0.3 represents an average level of functional connection strength (Supplementary Figure 1).

fNIRS experiment

The participants were guided to the experimental room, and seated on a wooden stool with a wooden table. During the experimental preparation phase, the participants were asked to wear an electrode cap. The experimenter repeatedly adjusted the electrode cap to maximize the signal channel gain. When the experiments begin, participants performed the task by listening to the instruction (verbal fluency task) or using an ipad (working memory task), as our previous work[8].



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Figure 1 Diagrammatic sketch of localization of the functional near-infrared spectroscopy probe set over left and right frontotemporal cortex. A: Anterior view; B: Lateral view; C: Probe arrangement. Blue circle: Detectors; Purple circle: Light source.

Data analysis

The NirSpark software package (Danyang Huichuang Medical Equipment Co. Ltd, China) was used to analyze the fNIRS data, as previously described[37-39]. Physiological noises (including respiration, cardiac activity, and low-frequency signal drift) were corrected by a band-pass filter with cutoff frequencies of 0.01-0.20 Hz. The cubic spline interpolation method was adopted to eliminate motion artifacts. The modified Beer-Labert law was used to convert the optical density into changes in oxy-Hb and deoxy-Hb concentrations. A general linear model was used to calculate brain activation strength. Functional connectivity was calculated by conducting Pearson's correlation analysis between the time series of every pair of measurement channels.

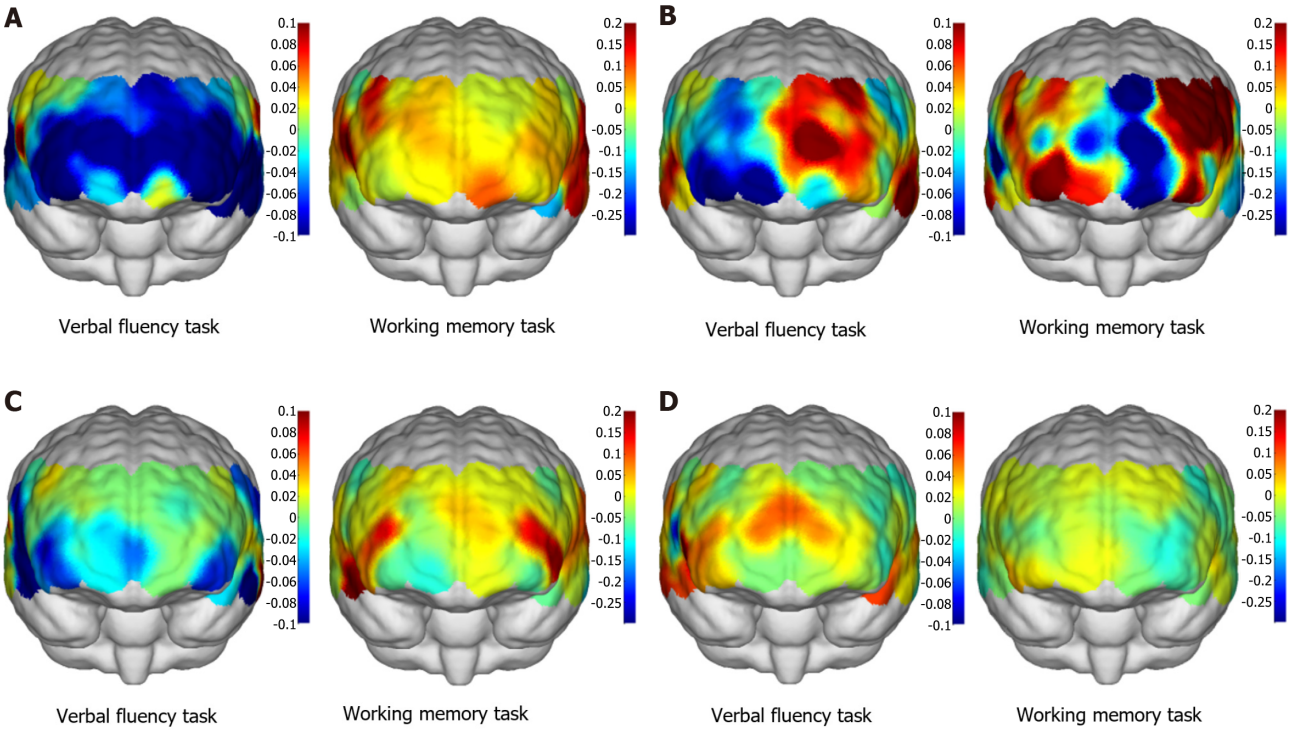
RESULTS

Subject 1 FTD

Clinical manifestation: A 57-year-old man was diagnosed with FTD. Two years prior, the patient began to show impaired judgment without warning and was defrauded of 700000 yuan. He reported insomnia, anxiety, and depression. His mental state continued to deteriorate, and he was initially diagnosed with "recurrent depressive disorder". He also exhibited memory problems such as being unable to recall whether he had eaten or not, and he was often unable to complete tasks assigned to him by his family. For the past 2 years, the patient had been treated with systematic antidepressants (such as sertraline, doxetine, mirtazapine) and modified electroconvulsive therapy. His depression partially eased, but his memory problems persisted. One month previously, the patient again showed nervousness and fidgeting. The patient also experienced hallucinations, slow walking, and involuntary limb shaking. He had been admitted to the neurology department, who had ruled out Parkinson's disease before he was admitted to our department for further treatment.

Examinations: The patient's psychiatric examination at admission showed clear consciousness, accurate orientation, lack of cooperation, less autonomous language, decreased language expression ability, poor vocabulary, stereotypes and imitation speech, stable mood, no obvious manifestations of emotional depression, and partial decline in memory intelligence. Physical examination revealed that the patient's right lower limb twitches could be relieved after massage. A brain MRI showed cystic foci in the left medial temporal lobe and senile brain changes. His Mini-Mental State Examination (MMSE) score was 22/30. Considering to his education level of high school, the severity of dementia was moderate. The patient was diagnosed as FTD accompanied by mild depression.

fNIRS results: In Figure 2A, fNIRS showed global lower activation in frontotemporal lobe when the patient performed the verbal fluency task. This was consisted with his clinical manifestation of poor verbal function. During the working memory task, the patient's prefrontal lobe activation was lower than that of the temporal lobe, and the frontal lobe activation was also low. Frontalpolar and temporopolar area showed most activation than other regions. The overall pattern was different from other three subtypes of dementia. During a resting state, the average strength functional connection of



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Figure 2 Comparison of functional near-infrared spectroscopy patterns and task performances during the verbal fluency task (left) and the working memory task (right) between four types of dementia patients. A: Frontotemporal lobe dementia; B: Lewy body dementia; C: Parkinson's disease dementia; D; Alzheimer's disease. Red indicates higher activation, while blue indicates lower activation.

all channels was considered high at 0.559 as shown in Figure 3A.

Subject 2 LBD

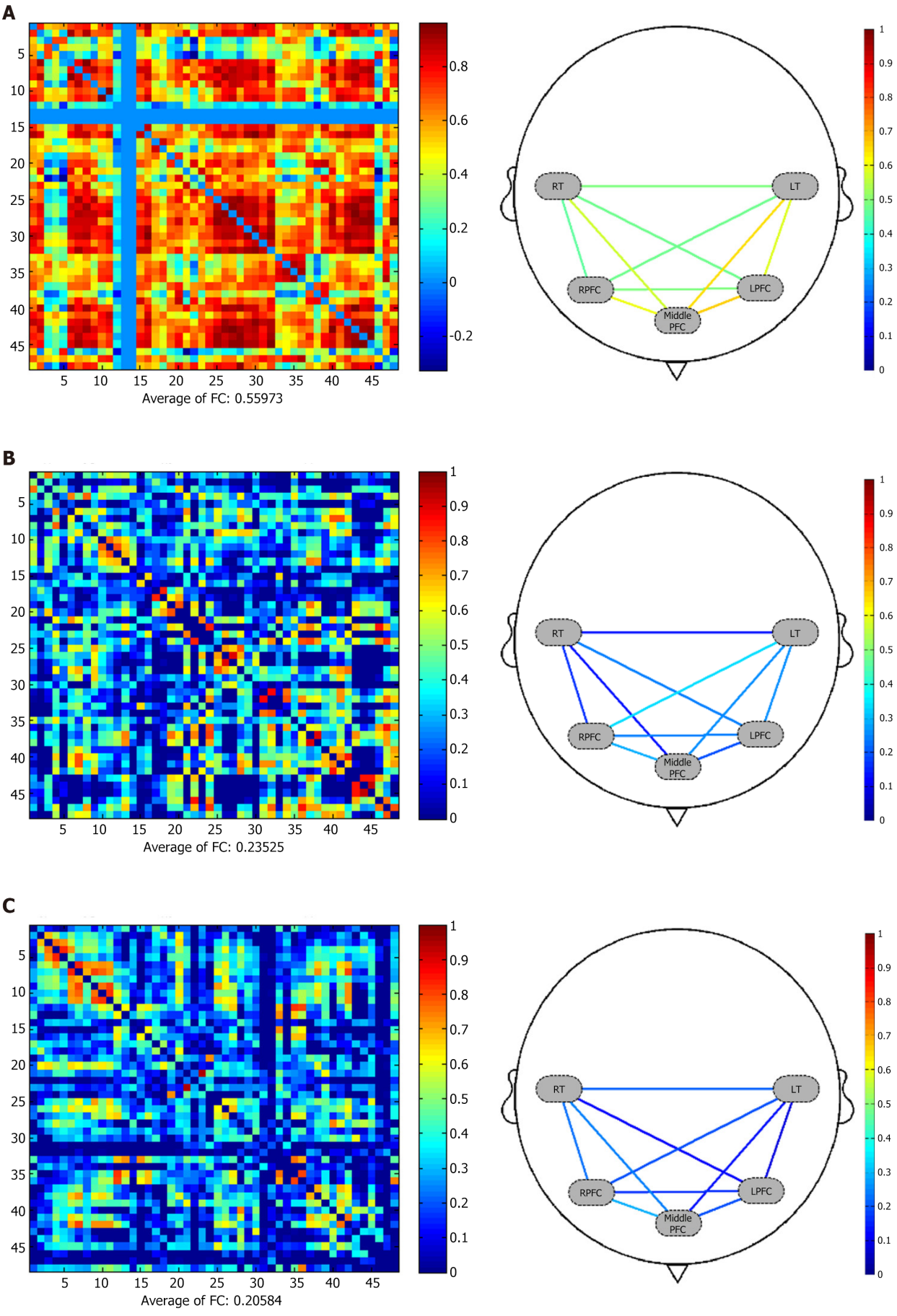
Clinical manifestation: A 74-year-old man was diagnosed with LBD. He had been experiencing progressive memory loss for three years, as well as symptoms such as hand shaking and bradykinesia; the neurology department considered him to have Parkinson's disease. Over three years, the patient's memory waxed and waned, while symptoms such as slow walking persisted. The patient occasionally experienced hallucinations such as seeing vivid images of dead people. In the last six months, his memory problem had significantly worsened; sometimes, he could not recall a family member's name. His speech was not very fluent, and he had difficulty communicating with others. His sleep was poor. His ability to perform daily living had significantly declined and he needed someone to take care of him.

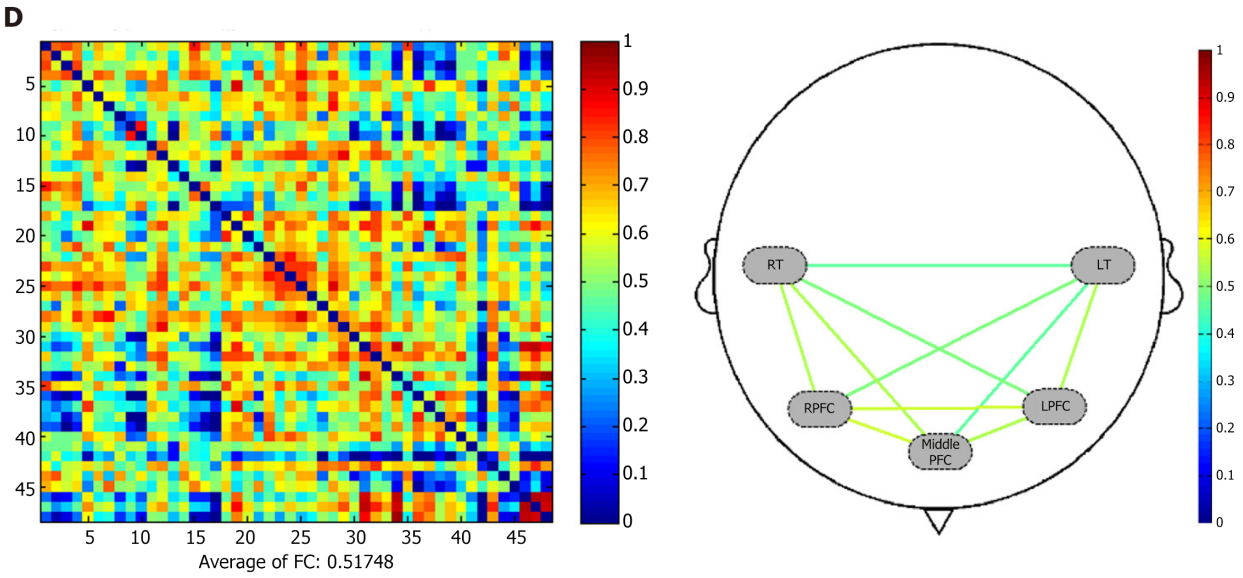
Examinations: The patient was admitted to our hospital for further treatment, and his psychiatric examination at admission showed clear consciousness, loss of sense of smell, unsteady gait, varying degrees of limb tremor, and increased muscle tone. He had slow thinking, aphasia, impaired memory, impaired common sense, reduced calculation ability, and visual hallucinations. A brain MRI showed localized atrophy in the temporal, frontal and parietal lobes. His MMSE score was 6/30. The degree of dementia was severe. The patient was diagnosed as primary neurodegenerative disease LBD.

fNIRS results: The fNIRS showed severe asymmetry in both hemispheres during both the verbal fluency and working memory tasks, particularly that the left frontal lobe showed more activation than the right lobe as shown in Figure 2B. In Figure 3B, the patient had low functional connection strength of 0.235 during a resting state.

Subject 3 PDD

Clinical manifestation: A 79-year-old man was diagnosed with PDD. Two years prior, the patient began to develop symptoms such as hand tremor and slow gait, and was subsequently diagnosed with "Parkinson's disease" by the neurology department. He was given symptomatic treatment of dopamine (0.0625 g tid) and pramipexole (0.25 mg bid) in oral form since then, and symptoms such as hand tremors and slow gait improved. About six months ago, his family reported development of memory problems. The patient forgot things immediately after being told, and forgot where he put things. His ability to perform daily tasks slowly declined, sometimes requiring family members to help him dress.


A
Average of FC: 0.55973
RT
LT
RPFC
LPFC
Middle PFC
B
Average of FC: 0.23525
RT
LT
RPFC
LPFC
Middle PFC
C
Average of FC: 0.20584
RT
LT
RPFC
LPFC
Middle PFC



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Figure 3 Resting state functional connections were calculated by conducting Pearson's correlation analysis between the time series of every pair of measurement channels. A: Frontotemporal lobe dementia; B: Lewy body dementia; C: Parkinson's disease dementia; D: Alzheimer's disease. Red indicates higher activation, while blue indicates lower activation.

Two months prior, the patient's mental state worsened due to sleep disorders and frequent nightmares. On occasion, he wakes in the middle of the night and begin to choke his wife. The patient was admitted for further treatment, and reported a family history of AD (in his sister).

Examinations: Upon mental examination, the patient's consciousness was clear. His recent memory decline was evidenced by his report of no memory of events after he went to bed. He gave simple answers to questions and demonstrated limited vocabulary and emotional instability, particularly irritability. His risk-taking behavior had increased, particularly in dangerous movements that may lead to falls or rejecting advice from others. CT showed multiple ischemic foci in both the frontal and parietal lobes and periventricular white matter. His MMSE score was 13/30. The degree of dementia was severe. The patient was diagnosed as typical PDD accompanied by sleep disorders.

fNIRS results: fNIRS showed that the patient's prefrontal cortex had lower excitability than the temporal lobe during the verbal fluency task, while the patient's prefrontal cortex had higher excitability during the working memory task. As shown in Figure 2C, the dorsolateral prefrontal cortex (DLPFC) was activated strongly (symmetrical pattern; in red color region) during the working memory task. During a resting state in Figure 3C, the average strength functional connection of all channels was 0.206, lower than the normal level.

Subject 4 AD

Clinical manifestation: A 73-year-old woman was diagnosed with dementia secondary to AD. About one year prior, the patient began to experience short-term memory loss, such as forgetting what she had said and done and failing to find the objects she had just placed. The ability to perform daily tasks declined slowly, requiring partial assistance from family members. The patient had a history of recurrent depressive disorder for approximately 10 years and long-term antidepressant treatment was moderately effective.

Examinations: The mental examination on admission found memory decline, computing power decline, orientation impairment, comprehension and expression ability decline, language vocabulary reduction, and emotional stability. A brain MRI showed reduced hippocampal volume and internal olfactory cortex volume bilaterally (MTA-score > 2). Her MMSE score was 14/30. The degree of dementia was moderate to severe due to her education level of 1 year. The patient was diagnosed as typical AD accompanied with mild depression.

fNIRS results: fNIRS revealed poor prefrontal and temporal activation during the working memory task (Figure 2D). The patient had high functional connection strength of 0.518 during a resting state (Figure 3D). The contrast of the two demented subjects (PDD *vs* AD) was characterized by a nearly symmetrical pattern in both task contrasts: prefrontal lobe was more activated in verbal fluency task in the AD than in PDD, while the frontotemporal lobe was more activated in working memory task in the PDD than in AD (Figure 2C and D). Regarding to the working memory task, the activation of brain in

AD was the weakest of four dementias.

DISCUSSION

The results of this study indicate that cortical activation measured with fNIRS while performing a verbal fluency and working memory task differs in patients suffering from four types of neurodegenerative dementia including FTD, LBD, PDD, and AD. Furthermore, this activation differs between the four types of neurodegenerative dementia, a result shown for the first time using fNIRS in antidiastole of dementia subtypes.

Patients with FTD show low function or atrophy of the frontotemporal lobe that may be accompanied by low levels of oxy-Hb low function of the frontotemporal lobe[40]. Although patients with FTD and those with psychiatric disorders behave similarly, differences can exist in hypoperfusion and hypometabolism of the frontotemporal lobe regions[41]. A reduction in cortical activation during verbal fluency task performance in FTD patient compared to other three dementias has been shown in this study. FTD disorders include behavioral variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA)[42]. PPA patients showed differential linguistic features of verbal fluency from bvFTD[43]. In this FTD case, the patient showed the poor verbal function. The fNIRS pattern showed low activation during the verbal fluency task. He had been treated with antidepressants. Currently, antidepressants are routinely used in the treatment of dementia to supplement serotonin availability[44]. There was no effect on vasculature at the relevant therapeutic dose for this patient, so it is unlikely that this affected blood flow in this patient. Furthermore, depressive pseudo dementia can also manifest as cognitive decline, but the brain functions, as well as neurovascular coupling, are not as poor in these patients compared to patients with dementia[45]. Thus, fNIRS can distinguish between depressive pseudo-dementia and dementia.

The AD pattern is weaker and more similar to the healthy pattern, whereas the bvFTD pattern is qualitatively different, namely more frontopolar and without frontoparietal compensation activation [18]. Our results showed the AD patient have lower and slower activation in the bilateral PFC and left parietal cortex during working memory maintenance. This was consisted with previous study on moderate to severe AD[2]. aMCI patients, as early stage AD, were reported a larger reduction in frontal deoxy-Hb during the memory task[46].

Regarding to the functional connection reflected by fNIRS, connections between different brain regions, as well as synergies between them, work together to provide comprehensive cognitive functions. As shown in Figure 3, the total scores of MMSE of patient with PDD and AD were similar in our study, but the functional connection strength is much different. The MMSE scale included six cognitive domains of orientation, immediately recall, attention, delayed recall, language and executive, and visual function[47]. Although the total MMSE scores of PDD and AD patients are close, they have different sub-scores in different cognitive domains, which reflect different brain area functions. In this aspect, the functional connectivity reflected by fNIRS can distinguish these differences, and enhanced the diagnostic accuracy as an auxiliary method.

The blood supply to the brain can reflect local changes in functional activity. In dementia patients, brain activity demonstrates a gradual increase in oxygenated hemoglobin and decrease in deoxygenated hemoglobin[48]. The working mode is believed to require networks across the entire brain; that is, no complex function is performed by a single brain area[6]. Imaging of the resting-state networks can also reveal information, such as the correlations between neural activities and the efficiency of transmission [49]. This is especially significant for patients with a low degree of cooperation[50]. Regarding to prefrontal cortex, primarily DLPFC, activation has a positive correlation with working memory load and performance until the working memory load exceeds the capacity[51].

fNIRS technology is widely used in the detection of neuropsychiatric disorders and brain functions individuals abusing different types of drugs[52-54]. Changes to oxy-Hb concentration of the bilateral prefrontal cortex in a schizophrenia group were reported to be significantly lower than those in a healthy group[55]. fNIRS has also been used to accurately distinguish patients with major depression from those with bipolar disorder or schizophrenia who have depressive symptoms[56]. When fNIRS technology was utilized to explore functional connectivity and network changes in patients with attention-deficit/hyperactivity disorder (ADHD), the development pattern of brain networks in children with ADHD was different from that of healthy children[57]. fNIRS also has applications in the field of sleep research to study brain activation during dreaming[49,57].

Limitations and future directions: one limitation is that a single patient for each group may introduce individual differences, including sex, age, and education. A larger sample size would help to eliminate the impact of such individual differences. Our results show that further study is needed to examine the diagnostic utility of fNIRS in dementia. Although our fNIRS recording technique was a multichannel flexible tool to detect the brain function in patients with different type of dementia, it focused on the frontal and temporal lobe of the brain, not the global brain region. This can be improved by using whole brain detection of fNIRS in the future.

CONCLUSION

Although subtypes of dementia may have similar clinical symptoms, they have different objective indicators; some that are observable during a resting state and some that are observable during the task state. Since fNIRS can detect changes in both states, it may be a useful tool for differential diagnosis. This study visualized four different types of dementia (FTD, LBD, PDD, and AD) using fNIRS, and found differences of brain activation during the task condition and functional connectivity during the resting state for all four types. The patient with FTD showed the lowest activation during the verbal fluency task and the patient with AD showed the lowest activation during the working memory task. During the resting state, functional connectivity was poor in the patients with LBD and PDD. These differences could be used as biomarkers to distinguish the different subtypes of dementia. In the future, as a non-invasive tool, multichannel fNIRS technology can provide high spatial and temporal resolution signals to continuously assess regional cerebral oxygenation. The sensitivity of fNIRS increased its use as a wide-spread clinical tool for the robust assessment of brain function.

ARTICLE HIGHLIGHTS

Research background

In addition to functional magnetic resonance imaging, electroencephalography, and event-related potentials, functional near-infrared spectroscopy (fNIRS) to examine functional connectivity between regions has become an important supplement to existing functional imaging technologies.

Research motivation

fNIRS technology will be widely used in the detection of neuropsychiatric disorders.

Research objectives

fNIRS could be a potential tool for the diagnosis between dementia subtypes.

Research methods

We tested four types of dementia by using fNIRS in the verbal fluency task, working memory task and resting state task.

Research results

fNIRS examinations were adopted to test the fNIRS paramters. The results shown that different types of dementia have different fNIRS patterns.

Research conclusions

fNIRS can be used as a potential method to diagnose dementia and cognitive decline.

Research perspectives

We want to study whether the fNIRS can be a potential tool for the diagnosis between dementia subtypes.

FOOTNOTES

Author contributions: Mei X and Zou CJ performed fNIRS protocols, data collection, and wrote the manuscript; Mei X, Zou CJ, Liu XL, and Hu J performed data analysis; Zheng CY and Zhou DS proofread the manuscript; all authors read and approved the final manuscript.

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Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: All data are included in the manuscript. However, the raw data used and/or analyzed in the

present study are available from the corresponding author on reasonable request.

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Observational Study

Estimated prevalence and sociodemographic correlates of mental disorders in medical students of Hebei Province, China: A cross-sectional study

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Abstract

BACKGROUND

In China, the identification rate and treatment rate of mental disorders are low, and there are few surveys on the prevalence of mental disorders among college students using diagnostic tools such as Mini-International Neuropsychiatric Interview (MINI), so the prevalence and treatment of mental disorders among college students are unclear.

AIM

To estimate prevalence of mental disorders among medical students in Hebei

Province, and provide guidance for improving their mental health.

METHODS

This was a cross-sectional study based on an Internet-based survey. Three levels of medical students in Hebei Province were randomly selected (by cluster sampling) for screening. Using the information network assessment system, the subjects scanned the 2D code with their mobile phones, clicked to sign the informed consent, and answered a scale. A self-designed general status questionnaire was used to collect information about age, gender, ethnicity, grade, and origin of students. The MINI 5.0. was used to investigate mental disorders. Data analysis was performed with SPSS software. Statistically significant findings were determined using a two-tailed *P* value of 0.05.

RESULTS

A total of 7117 subjects completed the survey between October 11 and November 7, 2021. The estimated prevalence of any mental disorders within 12 mo was 7.4%. Mood disorders were the most common category (4.3%), followed by anxiety disorders (3.9%); 15.0% had been to psychological counseling, while only 5.7% had been to a psychiatric consultation, and only 10% had received drug therapy in the past 12 mo.

CONCLUSION

Although the estimated prevalence of mental disorders in medical students is lower than in the general population, the rate of adequate treatment is low. We determined that improving the mental health of medical students is an urgent matter.

Key Words: Medical students; Estimated prevalence survey; Mental disorders; Mood disorders; Treatment rate

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Core Tip: College students' mental health is important to national mental health. In most previous studies of medical students, there have been few investigations using Mini-International Neuropsychiatric Interview (MINI) as a diagnostic tool to assess the prevalence of mental disorders. In this study, MINI 5.0 was used to investigate the prevalence of mental disorders among medical students in Hebei province, representing the largest series of mental disorders among medical students in China ever reported. Based on these data, the prevalence and treatment of mental disorders among medical students in Hebei were introduced.

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INTRODUCTION

From a sociological perspective, college students have a variety of social roles: they continue to seek knowledge, while developing social and interpersonal skills, and face more complex roles in society, personal relationships, and employment. With a growing number of college students in China, there is an increasing pressure in terms of learning, interpersonal relationships, and career decisions. Psychological health of college students has gradually become a focus of attention. In 2021, the General Office of the Ministry of Education issued a "Notice to Strengthen the Management of Students' Mental Health," which required the construction of a psychological counseling service platform. That year, the report "Exploring the Characteristic Service Plan for Prevention and Treatment of Depression" was issued by the General Office of the National Health Commission of China. This requires that depression screening should be included in students' physical examination.

Compared to the general population, college students have the ability to assess their own mental health, and most will turn to the psychological counseling center at their school when they suspect that they have psychological problems[1]. The prevalence of depression and anxiety among college students

has increased compared with before the coronavirus disease 2019 (COVID-19) pandemic. According to a survey by Hong Kong researchers, the fraction of students with moderate to higher levels of depression was significant (40.0%), including general anxiety (50.7%)[2]. Kavvadas *et al*[3] found that depression and anxiety in college students increased in the past 2 years. Hossain *et al*[4] conducted a 15-mo longitudinal study of 1140 college students. They found that, with time, there was a 22.5% and 27.1% increase in depression and anxiety, respectively. Mental disorders have increased each year, suggesting the importance of regular assessment of mental health issues.

Despite many studies on students' mental health, most had shortcomings, such as small sample size or lack of complete and structured diagnostic interviews. Huang *et al*[5] conducted a nationwide survey on the prevalence of mental disorders, without inclusion of college students. There has been no large sample study on the mental health of medical students in Hebei Province. This study screened the prevalence of mental disorders among medical students and analyzed the psychosocial risk factors. This will provide some direction for college student mental health services in the future.

MATERIALS AND METHODS

Study design and sampling

This was a cross-sectional study based on the Internet. We screened medical undergraduates at a university in Hebei Province from October to November 2021, which was a relatively stable period for the COVID-19 pandemic in Shijiazhuang, and randomly selected three levels of students by cluster sampling. Freshmen (grade 1), sophomores (grade 2), and juniors (grade 3) were concentrated at school, and we selected two of the above three grades for random evaluation. Most students in the senior and fifth grades had completed internships and were scattered among several hospitals, and their grades were randomly selected for evaluation.

Assessment tools

The screening tool for this study was an information network evaluation system developed by Saitron Information Co. Ltd. (Cangzhou, Hebei, China). Subjects scanned the QR code and clicked to sign the informed consent. For screening information so stay confidential, subjects logged into the system with a virtual student number and their initials. A one-to-one correspondence between the virtual student number and the actual student number was kept by the instructor. Subjects could check screening results on their mobile phones, and physicians interpreted screening results on site. This allowed subjects to know their mental health status at any time.

A self-designed status questionnaire was used to collect the subjects' basic information: age, gender, nationality, grade, and region were included. The Mini-International Neuropsychiatric Interview (MINI) was translated into Chinese by Sheehan *et al*[6]. MINI is a structured interview that assesses 16 categories of mental disorders. Research shows that it has good reliability, validity, and high consistency among different studies. The version used in this study was MINI 5.0.

Quality control

The screening staff comprised physicians and medical students from the Mental Health Center of Hebei Medical University. Before participating in the survey, screening personnel were trained with standardized guidelines, developed to ensure consistency of survey results. Some students were randomly selected for pretesting before formal screening. We summarized and revised ambiguities, using PowerPoint to explain subjects' biases, and to reduce biased screening.

Statistical analysis

Quantitative data were expressed as mean ± SD, and qualitative data were described by numbers and percentages. Comparison between groups with theoretical frequency $T \geq 5$ was tested by Pearson's χ^2 test; comparison between groups with theoretical frequency < 5 but ≥ 1 was tested by continuity correction χ^2 test; and comparison between groups with theoretical frequency < 1 was tested by Fisher's exact test. All data were analyzed using SPSS version 26.0 (SPSS, Chicago, IL, United States). The statistical significance of our findings was assessed with a two-tailed P value of 0.05.

Ethical approval

This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University (approval No: 20210354).

RESULTS

A total of 7555 undergraduates from three grades were selected for MINI assessment; 218 refused to participate in the screening and 7337 were screened. A total of 163 students with incomplete data and 57

with inaccurate data caused by careless attitudes in answering questions were excluded. Finally, 7117 students were included in the statistical analysis. The average age was 19.9 ± 2.06 years, with 36.7% males and 63.3% females. There were 3471 sophomores, 2974 juniors and 672 seniors (Table 1).

Among medical students in Hebei Province, 7.4% suffered from at least one mental disorder in the past 12 mo, 15.0% had psychological counseling, 5.7% went to a psychiatric hospital, and only 10% received drug treatment. Mood disorders were the most common category, followed by anxiety disorders. Lifetime estimated prevalence of each subcategory of mood disorders ranged from 0.5% to 4.9%, with the 12-mo estimated prevalence ranging from 0.2% to 3.5%. Major depressive disorder (MDD) was the most prevalent mood disorder (lifetime estimated prevalence 4.9% with 12-mo estimated prevalence of 3.5%), followed by bipolar disorder (0.5% and 0.4%) and dysthymia (12-mo estimated prevalence of 0.2%). Obsessive–compulsive disorder (OCD) was the most common anxiety disorder (12-mo estimated prevalence of 2.1%), followed by generalized anxiety disorder (1.7%) and social phobia (1.4%). The estimated prevalence of other anxiety disorders was < 1%, with the lowest estimated prevalence being agoraphobia without panic disorder (0.1%). The 12-mo estimated prevalence of substance disorders ranged from < 0.1% to 0.4%, with alcohol abuse the most prevalent (0.4%) and substance abuse the lowest (< 0.1%). The estimated prevalence of any alcohol disorder was higher than that of any drug disorders (0.6% *vs* < 0.1%). Lifetime estimated prevalence of any type of schizophrenia was 0.2% and 30-d estimated prevalence was 0.1%. The 12-mo estimated prevalence of any eating disorder or antisocial personality disorder was < 0.1 (Table 2).

Among mood disorders, the estimated prevalence of MDD was 4.3% in males, and was higher than 3.1% in females. The estimated prevalence of bipolar disorder was 0.6% in males and 0.2% in females, with a significant difference. Among anxiety disorders, the estimated prevalence of OCD was 2.8% in males and 1.6% in females. For individual substance disorders, the estimated prevalence of alcohol abuse and dependence was higher in males than in females (0.5% *vs* 0.1% for alcohol dependence, 0.7% *vs* 0.2% for alcohol abuse). There was no significant gender difference for other diseases, except MDD (Table 3).

The estimated prevalence of MDD was 3.8% in sophomores, 2.9% in juniors, and 4.9% in seniors. There were significant differences between junior and senior college students. There was no significant difference in the estimated prevalence of some diseases among medical students from different areas of origin. Regarding the experiences of left-behind children, results showed that the estimated prevalence of individual substance disorders had different etiologies. The estimated prevalence of alcohol dependence in left-behind children was higher than in children without being left-behind (1.0% *vs* 0.2%). There were also significant differences in drug dependence and eating disorders, but the estimated prevalence of these diseases was < 0.1%.

For treatment, the rate of medical students who were in psychological counseling varied between 14.4% and 36.4%, whereas 36.4% of students with dysthymia had counseling, and 35.3% of medical students with psychotic symptoms had counseling. Moreover, 25% of patients with agoraphobia without history of panic disorder, 20% with panic disorder, 18.4% with compulsive disorders, and 16.4% with MDD had counseling. The proportion of students who visited a psychiatric hospital varied between 3.9% and 33.3%; of which 23.5% were for psychotic disorders, 20.0% for post-traumatic stress disorder (PTSD), 18.2% for MDD, 13.2% for bipolar disorder, and 8.8% for OCD. The rate of treatment in 12 mo varied between 9.1% and 33.3%, with 26.7% for PTSD, 33.3% for substance dependence, 15.8% for bipolar disorder, and 9.6% for MDD (Table 4).

DISCUSSION

The rapid development of the Chinese economy, along with a change in the learning and employment environment, may have caused an increase in pressure on college students. Medical students are a special group – as compared to college students, as they have more academic pressure, take a longer time to obtain a degree, and have less diversity, which can lead to pressure and increased mental disease. As such, it is critical to investigate such disorders among medical students.

It was also found that 7.4% of medical students in Hebei had suffered from one mental disorder over the past 12 mo, but only a few sought help with a healthcare professional, and fewer received adequate medication within 12 mo – contrary to previous results. The World Health Organization-World Mental Health International Undergraduate Program conducted an Internet-based self-assessment questionnaire among freshmen at 19 universities in eight countries. It included screening for the 12-mo prevalence of six common Diagnostic and Statistical Manual of Mental Disorders-IV psychiatric disorders (MDD, mania/hypomania, generalized anxiety disorder, panic disorder, alcohol use disorder, and substance use disorder). It was shown that 31% of students had at least one of these disorders within 12 mo, with 16.4% receiving psychiatric treatment[7]. Compared to this study, Winkler *et al*[8] found that the 12-mo prevalence was higher, possibly related to the survey population, the survey time, or the assessment tools. Previous studies found that depression and other diseases were more common in freshmen than for those in other grades. This study did not include freshmen, so prevalence could more easily be reduced[9].

Table 1 Participant demographics, *n* (%)

	Frequency (*n* = 7117)
Gender	
Male	2610 (36.7)
Female	4507 (63.3)
Grade	
Sophomore year	3471 (48.8)
Junior year	2974 (41.8)
Senior year	672 (9.4)
Nationality	
Han	6746 (94.8)
Ethnic minorities	371 (5.2)
Region	
Urban	4049 (56.9)
Rural	3068 (43.1)
Left-behind children	
Yes	306 (4.3)
No	6811 (95.7)

Unlike the findings of many western scholars, the estimated prevalence of drug abuse and eating disorders in this study was low[10,11]. This may have something to do with the differences between Chinese and western cultures. In terms of drug abuse, China has strict supervision on addictive drugs, so students have less exposure to addictive drugs. Moreover, medical students have some understanding of pharmacology and are more aware of the harm of drug abuse[12-14]. In terms of eating disorders, most medical students focus on finishing school and pay less attention to habitus index, so fewer of them lose weight through excessive dieting, which may explain the lower incidence of anorexia[15]. Medical students understand nutritional metabolism and the importance of regular diet, which may also explain the low prevalence of eating disorders[16].

The proportion of students seeking treatment was lower in this study compared to others. It mirrors national conditions in China: patients tend to have an insufficient appreciation of diseases associated with stigma, resulting in lower diagnosis and treatment rates[17,18]. In the future, it will be necessary to increase publicity about mental diseases and increase their understanding, so that individuals can objectively evaluate diagnosis and treatment rate. In previous studies, the 12-mo rate in the Chinese population was 9.3%, which was higher than in this study. This may be because the population was aged 18-24 years and did not include any other age groups. In addition, Yueqin *et al*[5] found that those aged 50-64 years had the highest prevalence of mental health problems. However, medical subjects with psychiatric symptoms, substance abuse, and other diseases that affect social function was consistently lower than for social personnel, with an overall prevalence slightly lower as well.

It is well-known that increasing targeted treatment for mental disorders (*e.g.*, anxiety disorders, affective disorders, and alcohol and drug abuse) is a recognized issue in academic circles. In this study, 58 (16.4%) of the 354 patients with depression had psychological counseling, 17 (4.8%) visited psychiatric hospitals, and 34 (9.6%) received adequate medication. Lu *et al*[19] examined the prevalence and treatment of depression in China in 2021 and found that of 1007 participants with a 12-mo history of depression, only 84 (weighted 9.5%) had received treatment at any facility: 38 (3.6%) were in specialized mental health groups, 20 (1.5%) in general medicine, two (0.3%) in public services, and 21 (2.7%) in complementary/alternative medicine. Only 12 (0.5%) of 1007 patients with depression received adequate treatment. In the medical student population, treatment was higher than in the general population. This may be attributed to how the school attends to students' mental health, with sufficient awareness of the disease. Premedical students better understand depression and take the initiative for both diagnosis and treatment. Yet, compared to other physical diseases, these measures are still low.

The 12-mo estimated rate of depression, OCD, and other mental diseases was higher in males than females, similar to the research of Li *et al*[20]. This could be a function of adolescent males being more likely to show symptoms of the MINI diagnosis, such that prevalence would gradually decrease with age. While comparing different grades, we found the detection rate of depression in seniors to be higher than in juniors, confirming results of previous research. It may be that the pressure of graduation, plus postgraduate entrance examinations, in tandem with COVID-19, may have led to increased depression

Table 2 Lifetime and 12-mo prevalence of mental disorders in medical students (*n* = 7117)

	Lifetime prevalence		12-mo prevalence	
	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)
Mood disorders				
Any mood disorders	95	1.3 (1.08-1.63)	307	4.3 (3.86-4.81)
Depressive disorders	354	4.9 (4.48-5.51)	260	3.7 (3.23-4.12)
Major depressive disorder	354	4.9 (4.48-5.51)	249	3.5 (3.09-3.96)
Dysthymic disorder			11	0.2 (0.08-0.28)
Bipolar disorder	38	0.5 (0.38-0.74)	26	0.4 (0.24-0.55)
Anxiety disorders				
Any anxiety disorders	17	0.2 (0.14-0.39)	278	3.9 (3.48-4.39)
Panic attack	35	0.5 (0.35-0.69)	18	0.3 (0.15-0.40)
Agoraphobia without history of panic disorder			8	0.1 (0.05-0.23)
Social phobia			97	1.4 (1.11-1.66)
Obsessive–compulsive disorder			147	2.1 (1.76-2.44)
Post-traumatic stress disorder			15	0.2 (0.12-0.36)
Generalized anxiety disorder			118	1.7 (1.38-1.99)
Substance-use disorders				
Any substance-use disorders			46	0.7 (0.48-0.87)
Alcohol use disorders			42	0.6 (0.43-0.80)
Alcohol dependence			16	0.2 (0.13-0.37)
Alcohol abuse			26	0.4 (0.25-0.55)
Drug use disorders			4	< 0.1 (0.02-0.16)
Drug dependence			3	< 0.1 (0.01-0.13)
Drug abuse			1	< 0.1 (0.00-0.08)
Psychotic disorder				
Any psychotic disorder	17	0.2 (0.14-0.39)	5	0.1 (0.03-0.17)
Eating disorders				
Any eating disorders			4	< 0.1 (0.01-0.13)
Anorexia			3	< 0.1 (0.01-0.13)
Bulimia			1	< 0.1 (0.00-0.08)
Personality disorder				
Antisocial personality disorder	2	< 0.1 (0.01-0.12)		

in the population and in undergraduate students as well[21].

We found that the estimated prevalence of alcohol dependence and abuse was higher in males than in females. This is consistent with previous research. It may be that males make friends more quickly when drinking at parties, and drinking with a greater preference for alcohol[22-24]. We also found that the estimated prevalence of alcohol dependence among those who were left-behind was higher than among people who did not have that experience. Left-behind children deal with emotional neglect and are more likely to engage in behaviors such as smoking and drinking, and then develop alcohol dependence [25].

The 12-mo estimated prevalence of mental disorders, according to MINI (7.4%), is low, considering that the recognition and acceptance of mental disorders among medical students is higher than among other undergraduates. College students are the future of any nation, with a responsibility to promote social development, so that more attention is given to mental health; this also coincides with implementing effective intervention measures.

Table 3 12-mo prevalence of mental disorders by gender in medical students (*n* = 7117)

	Male		Female		*P* value
	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)	
Mood disorders					
Depressive disorders	114	4.4 (3.63-5.24)	146	3.2 (2.75-3.81)	0.014[a]
Major depressive disorder	111	4.3 (3.52-5.11)	138	3.1 (2.59-3.62)	0.008[b]
Dysthymic disorder	3	0.1 (0.03-0.36)	8	0.2 (0.08-0.37)	0.517
Bipolar disorder	15	0.6 (0.33-0.96)	11	0.2 (0.13-0.45)	0.026[a]
Anxiety disorders					
Panic attack	7	0.3 (0.12-0.58)	11	0.2 (0.13-0.45)	0.845
Agoraphobia without history of panic disorder	4	0.2 (0.05-0.42)	4	0.1 (0.03-0.25)	0.434
Social phobia	42	1.6 (1.18-2.19)	55	1.2 (0.93-1.60)	0.173
Obsessive compulsive disorder	73	2.8 (2.22-3.53)	74	1.6 (1.30-2.07)	0.001[b]
Post-traumatic stress disorder	7	0.3 (0.12-0.58)	8	0.2 (0.08-0.37)	0.421
Generalized anxiety disorder	46	1.8 (1.31-2.36)	72	1.6 (1.26-2.02)	0.599
Substance-use disorders					
Alcohol use disorders	30	1.2 (0.79-1.66)	12	0.3 (0.15-0.48)	< 0.001[b]
Alcohol dependence	13	0.5 (0.28-0.88)	3	0.1 (0.02-0.22)	< 0.001[b]
Alcohol abuse	17	0.7 (0.39-1.06)	9	0.2 (0.10-0.39)	0.002[b]
Drug use disorders	2	< 0.1 (0.01-0.31)	2	< 0.1 (0.01-0.17)	0.580
Drug dependence	2	< 0.1 (0.01-0.31)	1	< 0.1 (0.01-0.13)	0.281
Drug abuse	0		1	< 0.1 (0.00-0.14)	0.447
Psychotic disorder					
Any psychotic disorder	3	0.1 (0.03-0.36)	2	< 0.1 (0.01-0.17)	0.279
Eating disorders					
Anorexia	1	< 0.1 (0.00-0.25)	2	< 0.1 (0.01-0.17)	0.904
Bulimia	0		1	< 0.1 (0.00-0.14)	0.447

[a]$P < 0.05$ (male *vs* female).
[b]$P < 0.01$ (male *vs* female).

Our study had some limitations. First, subjects were medical students, excluding other college students, and there was also some selection bias in overall estimation of college students. Second, this study was cross-sectional, so that there may have been recall bias that affected the lifetime prevalence of mental disorders.

CONCLUSION

Our study provided supplemental data on mental health disorders in the medical students, not investigated by Huang *et al*[5]. College students' mental health is important to national mental health. The purpose of this study was to establish mental health records for students, and psychiatrists were involved in the whole screening process. Our mental health department has opened a convenient channel for students diagnosed with mental diseases by MINI 5.0. Students can voluntarily go to the hospital for treatment, and psychiatrists will give more comprehensive examination and evaluation at any time. We will thus expand our research in exploring the prevalence of mental disorders in other college students, followed by more information on mental health care for Chinese students in general.

Table 4 Health care treatment in the past 12 mo of medical students with mental disorders (*n* = 7117)

	Psychological consultative center		Psychiatric specialty hospital		Treatment	
	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)
Mood disorders						
Major depressive disorder	58	16.4 (12.76-20.75)	17	4.8 (2.91-7.72)	34	9.6 (6.83-13.28)
Dysthymic disorder	4	36.4 (12.36-68.38)	2	18.2 (3.21-52.24)	1	9.1 (0.48-42.88)
Bipolar disorder	6	15.8 (6.59-31.93)	5	13.2 (4.95-28.89)	6	15.8 (6.59-31.93)
Anxiety disorders						
Panic attack	7	20.0 (9.06-37.46)	6	17.1 (7.17-34.29)	8	22.9 (11.05-40.56)
Agoraphobia without history of panic disorder	2	25.0 (4.45-64.42)	2	25.0 (4.45-64.42)	2	25.0 (4.45-64.42)
Social phobia	14	14.4 (8.40-23.37)	7	7.2 (3.20-14.80)	8	8.3 (3.89-16.07)
Obsessive compulsive disorder	27	18.4 (12.66-25.78)	13	8.8 (4.98-14.94)	20	13.6 (8.71-20.47)
Post-traumatic stress disorder	5	33.3 (12.99-61.31)	3	20.0 (5.31-48.63)	4	26.7 (8.92-55.17)
Generalized anxiety disorder	19	16.1 (10.21-24.26)	13	11.0 (6.23-18.44)	13	11.0 (6.23-18.44)
Substance-use disorders						
Alcohol dependence	3	18.8 (4.97-46.31)	1	6.3 (0.33-32.29)	1	6.3 (0.33-32.29)
Alcohol abuse	4	15.4 (5.04-35.72)	1	3.9 (0.20-21.59)	3	11.5 (3.03-31.28)
Drug dependence	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)
Drug abuse	0		0		0	
Psychotic disorder						
Any psychotic disorder	6	35.3 (15.26-61.38)	4	23.5 (7.82-50.24)	2	11.8 (2.06-37.74)
Eating disorders						
Anorexia	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)
Bulimia	0		0		0	
Personality disorder						
Antisocial personality disorder	0		0		0	

ARTICLE HIGHLIGHTS

Research background

In China, the identification rate and treatment rate of mental disorders are low, and there are few surveys on the prevalence of mental disorders among college students using diagnostic tools such as Mini-International Neuropsychiatric Interview (MINI), so the prevalence and treatment of mental disorders among college students are unclear.

Research motivation

To clarify the prevalence and treatment of mental disorders in college students, and to provide protection for their mental health.

Research objectives

This study firstly conducted diagnostic assessment for medical students to understand the estimated prevalence and treatment of medical students, so as to provide protection for the mental health of medical students.

Research methods

MINI 5.0 was used in this study to evaluate medical students in Hebei and collect their treatment information, which can provide a more accurate understanding of the prevalence and treatment rate of

mental disorders.

Research results

Among medical students in Hebei Province, 7.4% suffered from at least one mental disorder in the past 12 mo, 15.0% had psychological counseling, 5.7% went to a psychiatric hospital, and only 10% received drug treatment.

Research conclusions

The results of screening for prevalence using MINI have high confidence. The estimated prevalence rate of mental disorders among medical students in Hebei is lower than that of the general population, but the treatment rate is also lower. In the future, it is necessary to increase the awareness of medical students to mental diseases and improve the treatment rate, so as to ensure their mental health.

Research perspectives

In the future, the scope of screening should be gradually expanded to more than one university, so as to comprehensively understand the prevalence of mental disorders among college students, and contribute to the development of mental health field.

FOOTNOTES

Author contributions: Wang XY was the guarantor and designed the study; Lu WT and Hu PH participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; An CX, Li N, Wang L, Wang R, Song M revised the article critically for important intellectual content; Zhao TY, Guo SJ, Huang FF, Liu BF, Ren RJ, Yang L, Lin Q, Xu YH, Jin N, Chen H and Gao YY participated in the acquisition of the data; Wang Z, Wu ZF and Shi GY involved in organizing the students to conduct the test and participated in the acquisition of the data; Liu DP, Pan ZQ and Du CC were responsible for software technical support and participated in the acquisition of the data.

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ORIGINAL ARTICLE

Observational Study

Effect of hyperbaric oxygen on post-stroke depression

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Abstract

BACKGROUND

In patients with post-stroke depression (PSD) in diabetes, the situation may be more complex, requiring simultaneous treatment of blood glucose, depressive symptoms, and neurological dysfunction. Hyperbaric oxygen (HBO) therapy can improve tissue oxygen content and improve the situation of ischemia and hypoxia, thus playing a role in protecting brain cells and restoring the function of brain cells. However, there are few studies on HBO therapy for patients with PSD. This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

AIM

To evaluate the clinical effects of HBO therapy on patients with diabetes with PSD.

METHODS

A total of 190 diabetic patients with PSD were randomly divided into observation and control groups (95 patients per group). The control group received escitalopram oxalate 10mg once a day for eight weeks. In addition, the observation group was also given HBO therapy, once a day, five times a week, for eight weeks. The Montgomery Depression Rating Scale (MADRS), National Institutes of Health Stroke Scale (NIHSS), hypersensitive C-reactive protein, tumor necrosis factor (TNF)-α, and fasting glucose levels were compared.

RESULTS

There were no significant differences in age, sex, or depression course between the groups (P > 0.05). After HBO treatment, MADRS scores in both groups decreased significantly (14.3 ± 5.2), and were significantly lower in the control group (18.1 ± 3.5). After HBO treatment, NIHSS scores in both groups decreased significantly, and scores in the observation group (12.2 ± 4.0) decreased more than in the control group (16.1 ± 3.4), the difference was statistically significant (P < 0.001). The levels of hypersensitive C-reactive protein and TNF-α in both groups were significantly decreased, and the observation group was significantly lower than the control group (P < 0.001). Fasting blood glucose levels in both groups decreased significantly, and those in the observation group decreased more (8.02 ± 1.10) than in the control group (9.26 ± 1.04), with statistical significance (t = -7.994, P < 0.001).

CONCLUSION

HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with PSD, and reduce the levels of hypersensitive C-reactive protein, TNF-α and fasting blood glucose.

Key Words: Hyperbaric oxygen therapy; Post-stroke depression; Diabetes; Hypersensitive C-reactive protein; Tumor necrosis factor-α; Fasting plasma glucose

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Core Tip: Post stroke depression is one of the common complications of stroke patients. It affects stroke patients in the acute phase and also occurs in the rehabilitation phase, with an incidence rate of about 33%. However, many patients with post-stroke depression may still not be diagnosed and treated. It is currently believed that biological and psychological factors are involved in the occurrence and development of post-stroke depression. Risk factors of post-stroke depression include gender, psychiatric history, size and location of stroke, poor social support and degree of physical injury. Post-stroke depression may not only affect the emotional state and quality of life of patients, but also hinder the recovery of neurological function, and even increase the mortality of patients. Studies have shown that changes in ischemic hypoxia and brain cell damage are common mechanisms of stroke and post-stroke depression, so improving ischemic hypoxia may be an effective treatment. Diabetes is a chronic disease characterized by elevated blood sugar and other metabolic disorders. diabetes is associated with an increased risk of stroke and post-stroke depression.

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INTRODUCTION

Post-stroke depression (PSD) is a common complication in stroke patients, which can affect those in the acute stage and also occur in the convalescence stage, with an incidence of approximately 33%. However, many patients with PSD may remain undiagnosed and untreated[1]. Biological and psychological factors are currently believed to be involved in the occurrence and development of PSD[2]. Risk factors include gender, history of mental illness, size and location of stroke, poor social support, degree of physical impairment, and so on[3]. PSD may not only affect patients' emotional state and quality of life, but also hinder the recovery of neurological function and even increase patient mortality[4]. Studies have suggested that changes in ischemic hypoxia and brain cell damage are the common mechanisms of stroke and PSD, so improving ischemic hypoxia may be an effective treatment[5]. Diabetes is a chronic disease characterized by elevated blood glucose and other metabolic disorders, and is associated with increased risk of stroke and PSD[6]. Therefore, in patients with PSD in diabetes, the situation may be more complex, requiring simultaneous treatment of blood glucose, depressive symptoms, and neurological dysfunction. Hyperbaric oxygen (HBO) therapy can improve tissue oxygen content and improve the situation of ischemia and hypoxia, thus playing a role in protecting brain cells and restoring the function of brain cells[7]. However, there are few studies on HBO therapy for patients with PSD. This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

MATERIALS AND METHODS

Patients

From June 2018 to June 2021, a total of 190 diabetic patients with PSD diagnosed and treated in the General Hospital of Chinese PLA were recruited, all of whom met the diagnostic criteria of PSD. Inclusion criteria: (1) Patients aged ≥ 18 years in line with PSD[8]; (2) The vital signs were stable, and the clinical laboratory indicators related to stroke were basically normal; (3) No serious complications or comorbidities, normal consciousness, and cognition; and (4) Diabetes was diagnosed before stroke and in line with the diagnostic criteria of the American Diabetes Association in 2018[9]. Exclusion criteria: (1) Complicated with serious dysfunction of heart, liver, kidney, and other organs; (2) Complicated with malignant tumor and coagulation diseases; and (3) Failure to cooperate with treatment or adherence. The study protocol was approved by the Ethics Committee of the General Hospital of Chinese PLA, and all patients or their families were informed and signed the consent. Among the 190 patients, there were 52 males and 43 females in the control group, with an average age of 63.7 ± 9.3 years, 49.2 ± 14.5 d of depression and 5.9 ± 3.4 years of diabetes. There were 55 males and 40 females in the observation group, with an average age of 62.9 ± 6.1 years, 50.1 ± 12.6 d of depression and 5.6 ± 3.6 years of diabetes. Data on the patients' age, sex, smoking history, past disease history, and disease course were collected. The patients' height and weight were measured, and their body mass index (BMI) was calculated. Their blood pressure was measured in the resting state.

Patient grouping and treatment methods

The patients were divided into observation and control groups using the random number table method, with 95 patients in each group. Patients in both groups were given nutritional cerebrovascular application (including mecobalamin 0.5 mg), once a day, three times a week, intramuscular or intravenous injection, which can be increased or decreased according to age and symptoms, anti-platelet (thromboxane A2 inhibitor aspirin, 75-100 mg/time, Once a day), hypoglycemic [exenatide's initial dose is 5 μg twice a day, and can be increased to 10 μg twice a day after 1 mo of treatment according to the patient's clinical response; injections should be given within 60 min before breakfast and dinner (or before 2 main meals per day; Approximately 6 h or longer)] and other conventional treatments. The control group received oral escitalopram oxalate, 10 mg, once a day (Sichuan Kelun Pharmaceutical Co., Ltd.) for eight weeks., In addition to the oral drug regimen of the control group, the observation group received HBO therapy, once a day, five times a week, for eight weeks.

The HBO treatment was as follows: An HBO chamber (OxyHealth Europe, Vitaeris 320™) was pressurized for 20 min to reach 0.25 mpa. The patient then put on a mask and breathed pure oxygen for 40 min, breathing cabin air at 10-min intervals. Finally, patients decompressed for 30 min to normal pressure, and then left the cabin. Treatment was once a day, 10 times for a course of treatment, each course of intermittent 7-10 d, for a total of two months of observation.

Observation indicators

The following observation indexes were used to evaluate the efficacy before and after treatment: (1) Depression evaluation: The Montgomery Depression Rating Scale (MADRS) scale was used to evaluate patients' depression. The scale is divided into 10 items, with each item being rated from 1 to 6. On a scale of 0 to 60, the higher the score, the more severe the depression; (2) Neurological function evaluation: The National Institutes of Health Stroke Scale (NIHSS) scale was used to evaluate patients' neurological function. The scale includes 14 items, scored from 0 to 42. The higher the score, the more severe the neurological impairment; and (3) Measurement of hypersensitive C-reactive protein and tumor necrosis factor (TNF)-α: 10 mL of fasting venous blood was taken before and after treatment, and the upper serum was centrifuged after standing. Levels of the aforementioned were determined by enzyme-linked immunosorbent assay as per the manufacturer's instructions.

Statistical analysis

Enumeration data were expressed as frequencies (percentage) and the χ^2 test was used to assess differences between the two groups. mean ± SD was used to represent measurement data, and the difference between the two groups was assessed *via* *t*-test. The differences of MADRS score, NIHSS score, hypersensitive C-reactive protein, TNF-α and fasting blood glucose levels between the two groups before and after treatment were determined by *t*-test. $P < 0.05$ was considered statistically significant (bilateral), and IBM SPSS 21.0 was used for statistical analysis of the data.

RESULTS

General patient information

This study included 190 patients with diabetes and PSD. Patients in the observation group were aged 64.4 ± 9.4 years, and male patients accounted for 57.9% (55/95). The course of depression was 50.8 ± 15.3

d, and the course of diabetes was 6.2 ± 3.6 years. The proportion of patients with hypertension, coronary heart disease and hyperlipidemia was 54.7% (52/95), 38.9% (37/95) and 66.3% (63/95), respectively. BMI of patients in the observation group was 25.8 ± 3.8 kg/m^2, and systolic blood pressure was 139.2 ± 13.3 mmHg. In the observation group, 57 patients (60%) had ischemic stroke and 38 (40%) had hemorrhagic stroke. In the control group, the patients were aged 63.0 ± 9.2 years, 51.6% (49/95) male, the course of depression was 47.5 ± 13.4 d, and the course of diabetes was 5.7 ± 3.2 years. In the control group, 48.4% (46/95) had a history of hypertension, 33.7% (32/95) had a history of coronary heart disease, 54.7% (52/95) had a history of hyperlipidemia. The BMI of the control group was 26.2 ± 4.1 kg/m^2, and the systolic blood pressure was 137.6 ± 12.3 mmHg. In the observation group, 48 patients (50.5%) had an ischemic stroke and 47 (49.5%) had a hemorrhagic stroke. There were no significant differences in these characteristics between the two groups ($P > 0.05$, Table 1).

Depressive state and neurological function scores

Before treatment, the MADRS score of observation group (33.7 ± 5.0) was not statistically significant compared with the control group (33.0 ± 4.0, $P > 0.05$). After HBO treatment, the MADRS scores in both groups decreased significantly; that of the observation group (14.3 ± 5.2) was significantly lower than that of the control group (18.1 ± 3.5), and the difference was statistically significant ($P < 0.001$). Before treatment, the NIHSS score of the observation group (21.9 ± 4.1) was compared with the control group (21.0 ± 3.9), and there was no statistical significance ($P > 0.05$). After HBO treatment, NIHSS scores in both groups decreased significantly; scores in the observation group (12.2 ± 4.0) decreased more than those in the control group (16.1 ± 3.4), the difference being statistically significant ($P < 0.001$) (Table 2).

Levels of hypersensitive C-reactive protein and TNF-α

Before treatment, there was no statistical significance in the level of hypersensitive C-reactive protein in the observation group (7.71 ± 1.73) compared with the control group (7.43 ± 1.53, $P > 0.05$). After HBO treatment, the level in both groups decreased significantly, and the level in the observation group (2.87 ± 1.49) was significantly lower than that in the control group (4.52 ± 1.42); the difference was statistically significant ($P < 0.001$). Before treatment, there was no significant difference in TNF-α between the observation group (57.2 ± 13.6) and control group (58.6 ± 11.9, $P > 0.05$). After HBO treatment, TNF-α in both groups decreased significantly, and decreased more in the observation group (26.7 ± 12.5) than in the control group (33.9 ± 11.1), with statistical significance ($P < 0.001$) (Table 3).

Fasting blood glucose level

Before treatment, there was no significant difference in fasting blood glucose level between the observation group (10.96 ± 0.91) and control group (11.16 ± 0.93). After HBO treatment, the level decreased significantly in both groups, and that in the observation group decreased more than that in the control group (9.26 ± 1.04); the difference was statistically significant ($t = -7.994$, $P < 0.001$, Table 4).

DISCUSSION

We found that HBO therapy improved depressive symptoms and neurological dysfunction in patients with PSD, and reduced levels of hypersensitive C-reactive protein and TNF -α compared with the control group. It is worth noting that patients with diabetes and PSD who underwent HBO therapy had lower fasting glucose levels.

Stroke is an acute cerebrovascular disease with high disability and mortality rates, and PSD is a common complication that may affect nearly one-third of patients[10-12]. Importantly, PSD not only affects the patient's psychosis but may also affect the treatment effect and recovery of neurological dysfunction in patients with stroke, and even increase the incidence of recurrent stroke and all-cause mortality[13,14]. Diabetes, a chronic disease mainly characterized by elevated blood glucose, may increase the risk of stroke and PSD[15,16]. Additionally, PSD combined with diabetes may increase the risk of recurrent stroke, aggravate depressive symptoms, and even increase patient mortality[17]. Therefore, diabetes is a major cause of stroke. With the development of diabetes, patients are prone to metabolic abnormalities, cholesterol will be further increased, and thrombosis will be formed, finally leading to ischemic stroke[18]. Timely control of blood glucose is an important prevention of stroke.

Currently, escitalopram is the main first-line drug for the treatment of PSD, and the use of this drug can improve patients' emotional symptoms, but studies have demonstrated that some patients with PSD still have depressive symptoms after using escitalopram, with poor efficacy[19]. Treatment includes changing the antidepressant, adding another antidepressant, or augmenting the treatment by adding another drug, such as an atypical antipsychotic or lithium. Non-pharmacological forms of augmentation of depression treatment have also been proven to be effective, including cognitive-behavioral psychotherapy, psychoeducation, aerobic exercise, neuromodulatory treatment through vagus nerve stimulation, electroconvulsive therapy (ECT), transcranial direct current stimulation (TDCS), repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation and light therapy; however, non-pharmacological forms of biological treatment used in the treatment of treatment-resistant depression

Table 1 Clinical characteristics of patients in two groups, *n* (%)

Clinical characteristics	Observation group	Control group	t/χ^2	*P* value
Patients	95	95	-	-
Age (yr)	64.4 ± 9.4	63.0 ± 9.2	1.052	0.294
Male	55 (57.9)	49 (51.6)	0.765	0.382
Depressive course (d)	50.8 ± 15.3	47.5 ± 13.4	1.579	0.116
Smoking history	38 (40.0)	31 (32.6)	1.115	0.291
Diabetes course (yr)	6.2 ± 3.6	5.7 ± 3.2	0.941	0.348
History of hypertension	52 (54.7)	46 (48.4)	0.759	0.384
History of coronary heart disease	37 (38.9)	32 (33.7)	0.569	0.451
History of hyperlipidemia	63 (66.3)	52 (54.7)	2.666	0.103
Body mass index (kg/m^2)	25.8 ± 3.8	26.2 ± 4.1	-0.676	0.500
Systolic blood pressure (mmHg)	139.2 ± 13.3	137.6 ± 12.3	0.873	0.384
Stroke type			1.724	0.189
Ischemic stroke	57 (60.0)	48 (50.5)		
Hemorrhagic stroke	38 (40.0)	47 (49.5)		

Table 2 Depressive state and neurological function scores of the two groups

Group	Patients	MADRS scores		NIHSS scores	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	95	33.7 ± 5.0	14.3 ± 5.2[a,d]	21.9 ± 4.1	12.2 ± 4.0[a,d]
Control group	95	33.0 ± 4.0	18.1 ± 3.5[a]	21.0 ± 3.9	16.1 ± 3.4[a]

[a]*P* < 0.001 *vs* before treatment in this group.
[d]*P* < 0.001 *vs* control group after treatment.
MADRS: Montgomery Depression Rating Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 3 The levels of hypersensitive C-reactive protein and tumor necrosis factor-α in the two groups

Group	Patients	Hypersensitive C-reactive protein (mg/L)		Tumor necrosis factor-α (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	95	7.71 ± 1.73	2.87 ± 1.49[a,d]	57.2 ± 13.6	26.7 ± 12.5[a,d]
Control group	95	7.43 ± 1.53	4.52 ± 1.42[a]	58.6 ± 11.9	33.9 ± 11.1[a]

[a]*P* < 0.001 *vs* before treatment in this group.
[d]*P* < 0.001 *vs* control group after treatment.

also do not show substantial efficacy. Despite the improvement achieved during electroshocks, ECT has no lasting effect, and despite continued pharmacotherapy, relapses are observed in a large (37%) proportion of patients[20]. TDCS has been used with a moderate effect on depression, similar to rTMS, which also has moderate and short-term efficacy in improving mood and cognitive function in people with depression[21]. Light therapy has proven to be ineffective in enhancing the effects of antidepressants in both seasonal and recurrent depression[22]. Currently, HBO therapy is known to be an effective and safe method for treating PSD, which has been the subject of numerous studies. This study found that HBO therapy can improve depressive symptoms and neurological dysfunction in patients with PSD, specifically improving the blood supply to the lesion and facilitate the blood supply to the focal point of the stroke. Under the action of HBO, the phenomenon of counter-stealing blood will appear in the tissue, which is conducive to the blood supply to the ischemic lesion. Increase vertebrobasilar artery blood flow: Under HBO, the vertebrobasilar artery system is the only blood vessel that

Table 4 Fasting blood glucose levels of the two groups

Group	Patients	Before treatment	After treatment	*t* value	*P* value
Observation group	95	10.96 ± 0.91	8.02 ± 1.10	20.177	< 0.001
Control group	95	11.16 ± 0.93	9.26 ± 1.04	13.256	< 0.001
t value	-	-1.475	-7.994	-	-
P value	-	0.142	< 0.001	-	-

does not contract but dilates, thus increasing the blood supply and oxygen supply to the brain stem and reticular structure, which is conducive to the improvement of the patient's wakefulness and mood. HBO therapy was found to improve depressive symptoms and neurological dysfunction in patients with PSD. Similar to this study, a meta-analysis established that HBO treatment reduced NIHSS scores (mean difference = 2.77 points, 95%CI from 3.57 to 1.98 points, $P < 0.001$) and improved Hamilton Depression Scale scores (mean difference = 4.33 points, 95%CI from 4.82 to 3.84 points, $P < 0.001$)[7].

Ischemic anoxic injury may be a common initiating factor of stroke and PSD, and inflammatory processes may also be involved in the occurrence and development of depression. It has been suggested that patients with PSD had higher levels of TNF-α compared with non-depressed patients (25.65 ± 9.24 *vs* 17.29 ± 4.27, $P < 0.001$)[23]. In this study, diabetic PSD patients in the observation group had lower levels of hypersensitive C-reactive protein and TNF-α compared with the control group. This suggests that inflammatory factors can be used as biomarkers of PSD in patients with diabetes and may be effective early treatment targets[24]. Interestingly, the present study found that patients with PSD and diabetes who underwent HBO therapy had lower fasting glucose levels. Previous studies have suggested that HBO therapy can promote insulin secretion in patients with diabetes and enhance glucose uptake by brain cells[25].

This study has some limitations. Owing to the small sample size, fewer variables were collected, and the observation time was short. Large randomized controlled clinical trials are required to validate the role of HBO therapy in patients with diabetes and PSD.

CONCLUSION

In conclusion, HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with PSD, and reduce the levels of hypersensitive C-reactive protein, TNF-α and fasting blood glucose, which is worthy of clinical promotion.

ARTICLE HIGHLIGHTS

Research background

This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

Research motivation

Changes in ischemic hypoxia and brain cell damage are common mechanisms of stroke and post-stroke depression, so improving ischemic hypoxia may be an effective treatment. Diabetes is a chronic disease characterized by elevated blood sugar and other metabolic disorders. diabetes is associated with an increased risk of stroke and post-stroke depression.

Research objectives

This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

Research methods

Patients in both groups were given nutritional cerebrovascular application, once a day, three times a week, intramuscular or intravenous injection, which can be increased or decreased according to age and symptoms, anti-platelet, hypoglycemic and other conventional treatments. The control group received oral escitalopram oxalate, 10 mg, once a day for eight weeks., In addition to the oral drug regimen of the control group, the observation group received hyperbaric oxygen (HBO) therapy, once a day, five times

a week, for eight weeks. The HBO treatment was as follows: an HBO chamber was pressurized for 20 min to reach 0.25 mpa. The patient then put on a mask and breathed pure oxygen for 40 min, breathing cabin air at 10-min intervals. Finally, patients decompressed for 30 min to normal pressure, and then left the cabin. Treatment was once a day, 10 times for a course of treatment, each course of intermittent 7-10 d, for a total of two months of observation.

Research results

There were no significant differences in age, sex, or depression course between the groups. After HBO treatment, Montgomery Depression Rating Scale scores in both groups decreased significantly, and were significantly lower in the control group. After HBO treatment, National Institutes of Health Stroke Scale scores in both groups decreased significantly, and scores in the observation group decreased more than in the control group, the difference was statistically significant. The levels of hypersensitive C-reactive protein and tumor necrosis factor (TNF)-α in both groups were significantly decreased, and the observation group was significantly lower than the control group. Fasting blood glucose levels in both groups decreased significantly, and those in the observation group decreased more than in the control group, with statistical significance.

Research conclusions

HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with post-stroke depression, and reduce the levels of hypersensitive C-reactive protein, TNF-α and fasting blood glucose.

Research perspectives

The future research direction is mainly to study the influence of depression in diabetes patients.

FOOTNOTES

Author contributions: Guo H and Ge YR concepted the study; Guo H, Dong YB and Zhao XC collected the data; Guo H, Zhao XC, Wang JC and Ge YR contributed to the formal analysis; Guo H and Zhao XC contributed to the investigation; Guo H, Zhao XC and Su GL contributed to the methodology; Guo H, Zhao XC, Su GL and Dong YB supervised the study; Zhao XC validated the study; Guo H and Ge YR contributed to the visualization of the study; Guo H and Wang JC originally drafted the manuscript; Guo H, Ge YR, Wang JC and Dong YB reviewed and edited the manuscript.

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ORIGINAL ARTICLE

Observational Study

Associations between Borg's rating of perceived exertion and changes in urinary organic acid metabolites after outdoor weight-bearing hiking

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Abstract

BACKGROUND

Developing methods to monitor exercise load and evaluate body fatigue and muscle injury over time in hiking training remains a key problem to be solved. A widely used psycho-physical tool to assess the subjective perception of effort during exercise is Borg's rating of perceived exertion (BRPE) scale. Data on the relationships and validity of the BRPE compared to objectively assessed metabolic criteria are still lacking, especially urinary organic acid concentrations.

AIM

To verify whether the BRPE scale could be used in the prescription of outdoor hiking with weight-bearing and reveal the relationship between the BRPE scale and urinary physiological measures.

METHODS

Eighty-nine healthy men (average age: 22 years) were enrolled in a 40 km (6 h) hiking training exercise with a 20 kg load. After training, the BRPE scale (6-20) was completed. All participants were divided into three groups according to the rating of the BRPE scale. Urine samples were collected before and after training. Urinary myoglobin levels were measured immediately using the fluorescent immunoassay method. The remaining urine was subpacked and frozen for the subsequent detection of urinary organic acids using gas chromatography and mass spectrometry.

RESULTS

The contents of organic acids and myoglobin in urine were significantly increased after participants hiked 40 km (6 h) with a 20 kg load. Only orthogonal partial

least-squares discrimination analysis performed well in separating the group with a BRPE score of 6-12 from the group with a BRPE score of 13-20. Significant differences in the urine levels of several organic acids were observed between the two groups, and the heatmap also presented different metabolic profiles based on BRPE. According to the standard of a variable importance in the projection > 1, fold change > 1.5 and $P < 0.05$, 19 different metabolites of urinary organic acids were screened and enriched in pathways mainly including the citrate cycle (tricarboxylic acid cycle) and alanine, aspartate and glucose metabolism.

CONCLUSION

The BRPE scale identified significantly different urinary organic acid profiles between the higher and lower BRPE value groups, and, thus, could be used to monitor body fatigue in individuals participating in long-distance outdoor hiking with weight bearing.

Key Words: Borg's rating of perceived exertion; Urine; Organic acid metabolism; Exercise intensity; Myoglobin; Hiking

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Core Tip: Developing methods to monitor exercise load and evaluate body fatigue over time in endurance training is a key problem to be solved. Borg's rating of perceived exertion (BRPE) scale has been widely used as a psycho-physical tool to assess the subjective perception of effort during exercise. In this study, we aimed to verify whether the BRPE scale could be used in the prescription of outdoor hiking with weight-bearing and reveal the relationship between the BRPE scale and urinary physiological measures, particularly urinary organic acid concentrations. Underlying mechanisms related to body fatigue and metabolic disorders were also analyzed in this study.

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INTRODUCTION

Long-distance weight-bearing hiking in the field is an important part of physical training, that helps improve cardiopulmonary endurance and muscle endurance. Many countries use this type of exercise as an essential component of endurance training for soldiers[1,2]. In this process, an excessive exercise load may lead to fatigue accumulation, which imposes risks of physical and mental stress[3]. It represents an inconspicuous and gradual process. If overtraining continues, more severe injury in soft tissue or skeletal muscle will occur[4,5]. Therefore, developing methods to monitor exercise load and evaluate muscle injury and body fatigue over time remains a key problem to be solved.

Exercise tests have been conducted for more than 60 years[6]. Many indices, such as lactate, creatine kinase, and myoglobin, which are based on blood biochemical tests, have been applied during exercise monitoring[7,8]. However, these invasive tests with complex methodologies and high costs are difficult to implement in the field. Noninvasive tools and indices are needed to assess the intensity of physical activity during outdoor hiking exercise interventions.

A widely used psycho-physical tool to assess the subjective perception of effort during exercise is Borg's rating of perceived exertion (BRPE) scale[9-11]. It assesses the mental load of exercise with the subjective level of physical exertion. First, the subjective level of physical exertion is divided into scores ranging from 6-20[9]. Later, other rating methods, such as methods with 10 levels and 100 levels, also appeared[12,13]. A BRPE value of 10 times was used to estimate the heart rate of the trainer. The American College of Sports Medicine has suggested that the BRPE value may be considered to add precision to heart rate when monitoring exercise intensity and even replace it once the relationship between the heart rate and BRPE value is known for an individual[14]. With the advantages of simplicity, economy and strong operability, the BRPE scale facilitates the collection of training load data efficiently and conveniently. Many studies have revealed that the BRPE value is useful both in the prescription of alternated-intensity training exercises and continuous tests in a laboratory[15-17], underlining the strong relationships between the BRPE value and the indices of physiological strains. Nevertheless, only a few studies have been performed within a more ecologically valid environment.

Previous studies examining hiking have reported that the BRPE scale is significantly higher as load mass increases[18]. However, data revealing the relationships and validity of the BRPE value compared to objectively assessed metabolic criteria, especially urine organic acid concentrations, are still lacking.

In the present study, we examined the relationship between the BRPE scale and physiological measures (urinary organic acid metabolite and myoglobin levels) of exercise intensity after 40 km outdoor hiking with weight-bearing of approximately 20 kg. The aim of this study was to verify whether the BRPE score collected after hiking could be used to prescribe these training exercises.

MATERIALS AND METHODS

Participants

This study included 89 healthy young men (average age: 22 years, range from 18 to 24 years). Individuals with basic diseases, such as heart and lung disease, anemia, bone injury, and hypertension, and those who were taking drugs were excluded. Individuals with fever or musculoskeletal or soft tissue injury in the 7 d before hiking were also excluded. All participants signed the informed consent form. This study was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital (S2021-019-01).

Hiking walking settings

All participants experienced a hiking training exercise of 40 km with 20 kg carriages in plain areas. The whole training exercise lasted from 8:00 to 14:00. Two short 10-min breaks were allotted to supply water and a longer 30-min break was provided at 11:00 am for the prescribed lunch.

At the end of training, everyone truthfully completed the BRPE scale (Table 1), and urine samples were collected before and after training. The level of myoglobin in urine was measured immediately, and the remaining urine was separated and frozen at -80 °C for organic acid measurements.

Detection of the urine myoglobin concentration

According to the instructions of the myoglobin assay kit (fluorescence immunochromatography) (Beijing Danda Biotechnology Co., Ltd. Beijing, China), the level of myoglobin in urine was determined using a fluorescence immunoassay analyzer (Beijing Danda Biotechnology Co., Ltd. Beijing, China). First, information from the calibration card was input into the analyzer, and the standard curve of the urine sample type was selected. Then, the test card was removed, and 80 μL of the urine sample was added into the sampling hole of the test card. After 15 min, the test strip was placed into the dry fluorescent immunoassay analyzer to read the data. The chemical signal was measured and analyzed to quantitatively obtain the myoglobin concentration in the tested sample.

Detection of urine organic acids

Sample prehandling: One hundred microliters of urine was mixed with 30 μL of urease and incubated at 37 °C for 30 min. Next, 100 μL of the internal standard (margaric acid, 100 ppm) and 1 mL of absolute ethanol were added and the mixture was centrifuged at 13000 rpm for 5 min at 4 °C. The supernatant was extracted, and after adding 2% hydroxylamine hydrochloride, it was added to the supernatant, it was incubated at 60 °C for 10 min. After cooling at room temperature, the supernatant was transferred to a glass bottle and dried with nitrogen. Finally, 100 μL of BSTFA + TMCS (99:1) were added and incubated at 80 °C for 30 min, and gas chromatography and mass spectrometry (GC/MS, TSQ 8000 EVO, Thermo Scientific, United States) was used for the organic acid analysis.

GC/MS parameters: The chromatography column was a DB-5 column (30 m × 0.25 mm × 0.25 μm) purchased from Agilent Technologies Inc. The injection temperature and transfer line temperature were set to 250 °C and 290 °C, respectively. The injection volume was 1 μL, the split mode was selected with a ratio of 1:20, and the flow rate of high purity helium was 1 mL/min. The initial oven temperature was set to 100 °C and maintained for 4 min; then it was heated at a rate of 4 °C/min to 280 °C and maintained for 7 min.

GC/MS acquisition: Standard solutions (Zhejiang Biosan Biochemical Technologies Co., Ltd., China) of organic acids were prepared using the procedures described above and analyzed with a scan range of 50-550 m/z using Xcalibur software (ver. 2.1, Thermo Scientific, United States). The characteristic retention time and fragment ions of each organic acid were determined, and an organic acid database was established. Next, the instrument acquisition method was established by performing timed acquisition with the scan type of single iron monitoring (SIM). Timed acquired SIM data were analyzed using Trance Founder software (ver. 3.0, Thermo Scientific, United States). The GC/MS data of urine samples were qualitatively compared with the spectrometry database, and the final results were reported as the ratio of the peak area of the detected compound to the peak area of the internal standard.

Table 1 The Borg's rating of perceived exertion scale (6-20)

Score	Perceived exertion
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Statistical analysis

Data are presented as the means ± SD for normally distributed data or medians + interquartile ranges for nonnormally distributed data. For statistical comparisons, independent sample *t* tests or Mann-Whitney *U* tests (nonnormally distributed data) were performed using SPSS 25.0 and GraphPad Prism 8.0 software. SIMCA14.1.0 software was used for principal component analysis (PCA) and orthogonal partial least-squares discrimination analysis (OPLS-DA). Heatmaps and radar charts were processed on the Xiantao website (http://www.xiantao.love). The pathway analysis was performed using MetaboAnalyst 5.0 (https: //www.metaboanalyst.ca/).

RESULTS

Changes in organic acid and myoglobin levels before and after exercise

The volcano map of the results for organic acid metabolism before and after exercise is shown in Figure 1. Log2 (fold change) was set as the abscissa and -Log10 (*P* value) was set as the ordinate. The results showed that the levels of oxalic acid, pyruvic acid, 3-OH-butyric acid, 2-OH-isovaleric acid, 2-methyl-3-OH-butyric acid, benzoic acid, maleic acid, glyceric acid, fumaric acid, 3-methylglutaric acid, 3-methylglutaconic acid, glutaconic acid, decanoic acid, malic acid, adipic acid, creatinine, 2-OH-glutaric acid, pimelic acid, 2-ketoglutaric acid, phenylpyruvic acid, aconitic acid, vanillic acid, homovanillic acid, azelaic acid, citric acid, sebacic acid and palmitic acid were significantly increased after exercise. The myoglobin level was also increased after exercise ($P = 0.0133$).

Differentiation in the BRPE scale groups based on urinary organic acids

Figure 2 shows the PCA and OPLS-DA scores of the BRPE scale and urine organic acid levels. An unsupervised PCA was performed as the statistical analysis to evaluate the difference in organic acid metabolites among the groups with scores of 6-12, 13-16 and 17-20. PCA results showed no significant separation among the three groups. The supervised OPLS-DA model was subsequently used for analysis, and the results showed a clear separation between the groups with scores of 6-12 and 13-16 (Figure 3A) and between the groups with scores of 6-12 and 17-20 (Figure 3B). The model parameters of Q_2Y and R_2Y for those two group separations were 0.315 and 0.452 and 0.299 and 0.527, respectively. Although the groups with scores of 12-15 and 16-20 could not be separated (Figure 3C), the model parameters of Q_2Y and R_2Y were 0.0777 and 0.312, respectively.

Since the distinction between the groups with scores of 13-16 and 17-20 was not obvious, groups with scores of 13-16 and 17-20 were combined into one group (score of 13-20) for analysis. The OPLS-DA results showed that the two groups were separated (Figure 3D), and the model parameters of Q_2Y and R_2Y were 0.236 and 0.368, respectively. The statistical results also showed significant differences in the levels of most of the organic acid indicators between the two groups (Table 2).

Table 2 Change of Borg's rating of perceived exertion scale and organic acids

Compound	6-12 scale (*n* = 10), mean ± SD (range)	13-20 scale (*n* = 79), mean ± SD (range)	*t*	*P* value	Freedom	Effect size
Lactic acid	0.016 (0.013, 0.018), 0.008-0.038	0.028 ± 0.024 (0.010-0.150)	-2.933	0.006	32.954	-0.295
2-OH-isobutyric acid	0.003 ± 0.002 (0.001-0.006)	0.005 ± 0.003 (0.002-0.026)	-2.371	0.028	19.844	-0.279
Glycolic acid	0.246 ± 0.095 (0.098-0.393)	0.347 ± 0.115 (0.111-0.617)	-3.086	0.009	87	-0.431
2-OH-butyric acid	0.001 ± 0.000 (0.000-0.002)	0.002 ± 0.001 (0.001-0.008)	-5.425	0.000	26.692	-0.517
Glyoxylic acid	0.005 (0.004, 0.007), 0.004-0.010	0.009 (0.007, 0.011), 0.004-0.023	-4.554	0.000	14.629	-0.540
Oxalic acid	0.006 ± 0.003 (0.003-0.011)	0.008 ± 0.005 (0.000-0.031)	-1.382	0.182	20.192	-0.166
Pyruvic acid	0.026 ± 0.007 (0.013-0.036)	0.044 ± 0.021 (0.017-0.149)	-5.621	0.000	35.797	-0.503
3-OH-butyric acid	0.092 ± 0.035 (0.053-0.173)	0.219 ± 0.148 (0.054-1.025)	-2.689	0.009	87	-0.508
2-OH-isovaleric acid	0.007 ± 0.003 (0.004-0.013)	0.014 ± 0.009 (0.003-0.073)	-5.280	0.000	41.164	-0.468
2-methyl-3-OH-butyric acid	0.002 (0.002, 0.003), 0.001-0.015	0.004 (0.003, 0.006), 0.001-0.012	-3.159	0.002	87	-0.548
2-keto-isovaleric acid	0.001 ± 0.000 (0.000-0.001)	0.001 ± 0.001 (0.000-0.004)	-3.589	0.001	87	-0.614
Benzoic acid	0.001 (0.001, 0.001), 0.001-0.015	0.003 ± 0.002 (0.001-0.013)	-2.77	0.787	9.575	-0.056
2-keto-3-methylvaleric acid	0.001 ± 0.000 (0.000-0.001)	0.001 ± 0.001 (0.000-0.006)	-2.869	0.005	87	-0.535
Maleic acid	0.001 ± 0.000 (0.000-0.001)	0.001 ± 0.001 (0.000-0.003)	-4.047	0.001	16.432	-0.474
Succinic acid	0.007 ± 0.005 (0.002-0.019)	0.018 (0.013, 0.022), 0.005-0.032	-4.814	0.000	87	-0.673
Glyceric acid	0.003 ± 0.002 (0.001-0.006)	0.004 (0.003, 0.007), 0.002-0.014	-3.959	0.001	16.204	-0.468
Fumaric acid	0.019 ± 0.010 (0.004-0.042)	0.050 ± 0.030 (0.012-0.183)	-3.261	0.002	87	-0.573
Glutaric acid	0.002 ± 0.001 (0.000-0.004)	0.006 (0.004, 0.010), 0.002-0.018	-4.359	0.000	87	-0.684
3-methylglutaric acid	0.003 ± 0.003 (0.001-0.010)	0.006 (0.004, 0.009), 0.001-0.020	-3.262	0.006	13.322	-0.438
3-methylglutaconic acid	0.006 ± 0.004 (0.002-0.013)	0.016 ± 0.008 (0.004-0.043)	-6.149	0.000	19.746	-0.603
Glutaconic acid	0.006 ± 0.004 (0.001-0.014)	0.016 ± 0.011 (0.001-0.052)	-2.857	0.005	87	-0.516
Decanoic acid	0.000 (0.000, 0.001), 0.000-0.001	0.001 (0.001, 0.001), 0.000-0.004	-2.754	0.007	87	-0.486
Malic acid	0.002 (0.002, 0.004), 0.001-0.010	0.009 ± 0.008 (0.001-0.057)	-4.364	0.000	29.065	-0.429
Adipic acid	0.006 ± 0.007 (0.001-0.024)	0.019 ± 0.021 (0.003-0.123)	-3.932	0.000	35.442	-0.378
Creatinine	2.717 ± 3.056 (0.279-10.426)	5.955 ± 3.663 (0.012-13.452)	-3.157	0.008	12.488	-0.433
Mandelic acid	0.002 ± 0.002 (0.001-0.003)	0.003 ± 0.001 (0.001-0.007)	-5.460	0.000	15.516	-0.598
2-OH-glutaric acid	0.006 ± 0.003 (0.002-0.013)	0.017 ± 0.009 (0.000-0.044)	-3.867	0.000	87	-0.634
Pimelic acid	0.002 ± 0.001 (0.000-0.004)	0.005 ± 0.003 (0.000-0.014)	-3.978	0.000	87	-0.645
2-keto-glutaric acid	0.002 ± 0.003 (0.000-0.009)	0.020 ± 0.013 (0.000-0.087)	-4.268	0.000	87	-0.684
Phenylpyruvic acid	0.013 ± 0.008 (0.005-0.032)	0.034 (0.023, 0.043), 0.005-0.136	-7.031	0.000	31.925	-0.599
Aconitic acid	0.002 (0.001, 0.012), 0.000-0.028	0.053 ± 0.041 (0.001-0.174)	-8.287	0.000	64.322	-0.605
Vanillic acid	0.023 ± 0.025 (0.001-0.075)	0.035 (0.016, 0.080), 0.000-0.357	-3.146	0.004	27.007	-0.330
Homovanillic acid	0.011 (0.007, 0.017), 0.004-0.060	0.044 ± 0.022 (0.009-0.129)	-4.900	0.000	13.464	-0.588
Azelaic acid	0.008 ± 0.007 (0.000-0.022)	0.017 ± 0.012 (0.002-0.084)	-3.418	0.003	16.749	-0.410
Citric acid	0.001 ± 0.001 (0.000-0.003)	0.005 ± 0.005 (0.000-0.030)	-2.517	0.014	87	-0.487
Sebacic acid	0.078 (0.042, 0.168), 0.023-0.481	0.252 ± 0.183 (0.034-1.039)	-2.135	0.053	12.500	-0.316
Palmitic acid	0.025 ± 0.007 (0.014-0.033)	0.040 ± 0.012 (0.024-0.095)	-6.076	0.000	16.511	-0.627

Comparison of metabolic profiles in urinary metabolites between the low and high BRPE score groups

The heatmap cluster analysis (Figure 4) revealed the metabolic profiles of organic acids between the groups with scores of 6-12 (low BRPE score group) and 13-20 (high BRPE score group). The redder color represents a higher content. The urine contents of organic acids in the group with a score of 6-12 were generally low.

According to a fold change > 1.5, variable importance in the projection > 1 and $P < 0.05$ for organic acids, the differentially abundant compounds between the groups with scores of 6-12 and 13-20 were screened, and 19 differentially abundant compounds were identified (Table 3). A radar chart of these metabolites was then constructed based on the abundance of organic acids (Figure 5). Compared with the group with a score of 6-12, the organic acid levels in the group with a score of 13-20 were significantly increased. Because of the high order of magnitude for creatinine, which was significantly different from the other organic acids, the creatinine index was removed, and a radar chart without creatinine was constructed, as shown in Figure 5B. Figure 6 shows the metabolic pathways of the differentially abundant metabolites, and the results revealed significant differences in the metabolic pathways of the citrate cycle [tricarboxylic acid (TCA) cycle] and alanine, aspartate and glucose metabolism.

Correlation analysis between the BRPE score and myoglobin level

The statistical results for the myoglobin levels among the groups with BRPE scores of 6-12 and 13-20 are shown in Figure 7A. No significant differences were observed between the groups with scores of 6-12 and 13-20. The results of Spearman's analysis of the Borg scale showed no significant correlation between the Borg scale and myoglobin level (Figure 7B).

DISCUSSION

In this study, 89 healthy young men were enrolled in a 40 km (6 h) outdoor hiking training exercise. We compared urine organic acid and myoglobin levels before and after hiking and analyzed the underlying correlation between the BRPE score and urine organic acid levels.

The results showed that the levels of most of the organic acid metabolites increased after hiking. Organic acids are a class of carboxylic acids produced from amino acids, fats and carbohydrates in the metabolic process of the body, which directly participate in many biochemical reactions involved in life activities. They are also related to the metabolic activities and mutual transformation of sugar, fat and protein. Previous studies have shown an increased level of glycolysis products, such as TCA cycle intermediates, nucleotide products and branched-chain amino acids, which are usually related to energy metabolism, during endurance training[19-21].

Urine myoglobin levels were also detected before and after exercise. Myoglobin exists in cardiac muscle and skeletal muscle cells and has a close relationship with exercise-related fatigue and sports injury[22,23]. When exercise causes skeletal muscle injury, the content of myoglobin in blood or urine may consequently increase. Our results showed that urinary myoglobin levels increased after exercise but were within the normal range, indicating that exercise-related fatigue may have occurred after exercise, but we could not clearly determine what extent of fatigue occurred.

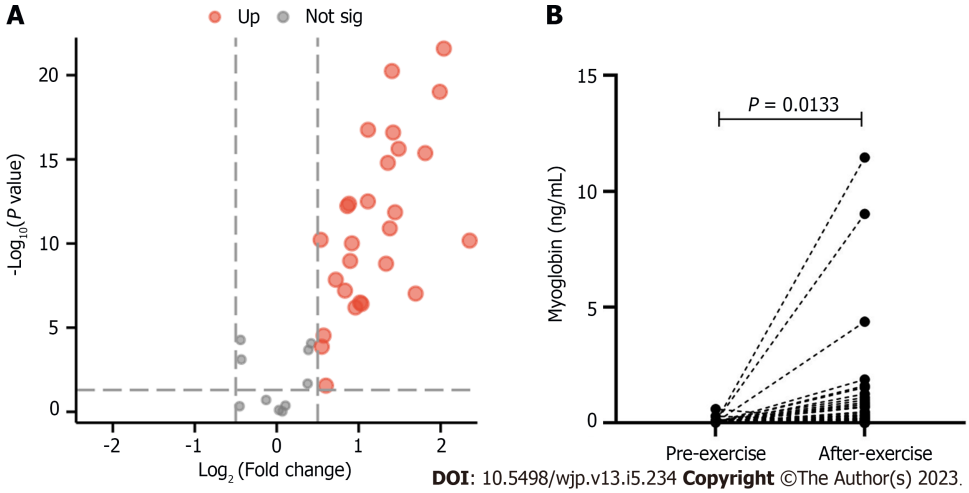
The BRPE scale is a simple method to quantify the degree of self-perceived exertion of the human body, particularly in fatigue evaluations[24,25]. We collected the BRPE scores of the trainees after exercise and divided them into groups with scores of 6-12, 13-16 and 17-20 according to self-perceived exertion measured using the BRPE scale. Only the supervised OPLS-DA model performed well in separating trends between groups. We observed that the 6-12 score group was significantly separated from the 13-16 and 17-20 score groups. However, the latter two groups were not separated because no obvious differences in metabolism were detected between the two groups. Therefore, we combined those two groups into a 13-20 score group. This result indicates that organic acid metabolism changed when "somewhat hard" was reported as a psychological perception of exercise. The heatmap of the BRPE score and organic acid metabolites directly showed that the contents of organic acids increased in the higher BRPE score group (13-20). These findings support the results of our study that individuals with higher BRPE values experienced more metabolic changes related to body fatigue. There is a need to individualize the recovery or training strategies in the same excises. Our study is the first to compare metabolomic responses controlled by the BRPE in hiking training. Our data indicate that for individuals undergoing the same training, the BRPE score may discriminate those with different stress ranges at a biochemistry level. This result is also consistent with previous research that the BRPE could show the relevance of individual recovery treatments and the sensitivity and predictability of metabolomics to prevent biochemical and physiological disturbances[26].

Then, we screened differentially abundant metabolites according to the multivariate and univariate statistical significance criteria. Nineteen differentially abundant metabolites identified between the groups with scores of 6-12 and 13-20 are shown in Table 3 and Figure 5. A subsequent pathway enrichment analysis showed that the TCA cycle and alanine, aspartate and glutamate metabolism were the main distinctive metabolomic characteristics in the 13-20 score group. The TCA cycle is the process

Table 3 Differential organic acid metabolites between Borg's rating of perceived exertion 6-12 scale and 13-20 scale

Compound	KEGG ID	VIP	Fold change	*P* value
Succinic acid	C00042	1.38	2.45	0.000
Homovanillic acid	C05582	1.29	2.76	0.000
Glutaric acid	C00489	1.27	3.52	0.000
Palmitic acid	C00249	1.25	1.64	0.000
3-methylglutaconic acid	-	1.21	2.64	0.000
Pimelic acid	C02656	1.19	3.54	0.000
2-keto-glutaric acid	C00026	1.19	8.52	0.000
2-OH-glutaric acid	-	1.18	3.00	0.000
Mandelic acid	C01984	1.16	1.91	0.000
Glyoxylic acid	C00048	1.15	1.63	0.000
3-methylglutaric acid	-	1.11	2.08	0.006
2-keto-isovaleric acid	-	1.09	2.01	0.001
Aconitic acid	C00417	1.08	7.11	0.000
Phenylpyruvic acid	C00166	1.08	2.92	0.000
Glutaconic acid	C02214	1.05	2.64	0.005
2-methyl-3-OH-butyric acid	-	1.04	2.00	0.002
2-OH-butyric acid	C05984	1.04	1.89	0.000
Fumaric acid	C00122	1.01	2.66	0.002
Creatinine	C00791	1.00	2.22	0.008

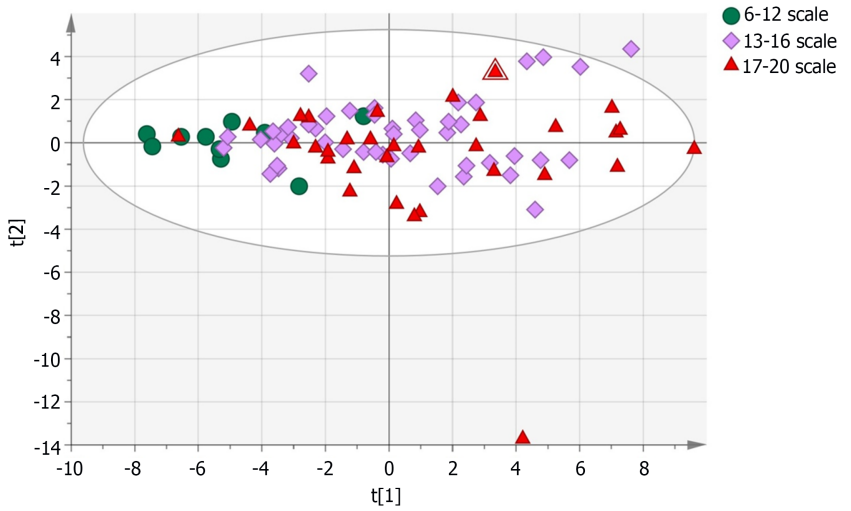
KEGG: Kyoto encyclopedia of genes and genomes; VIP: Variable importance in the projection.



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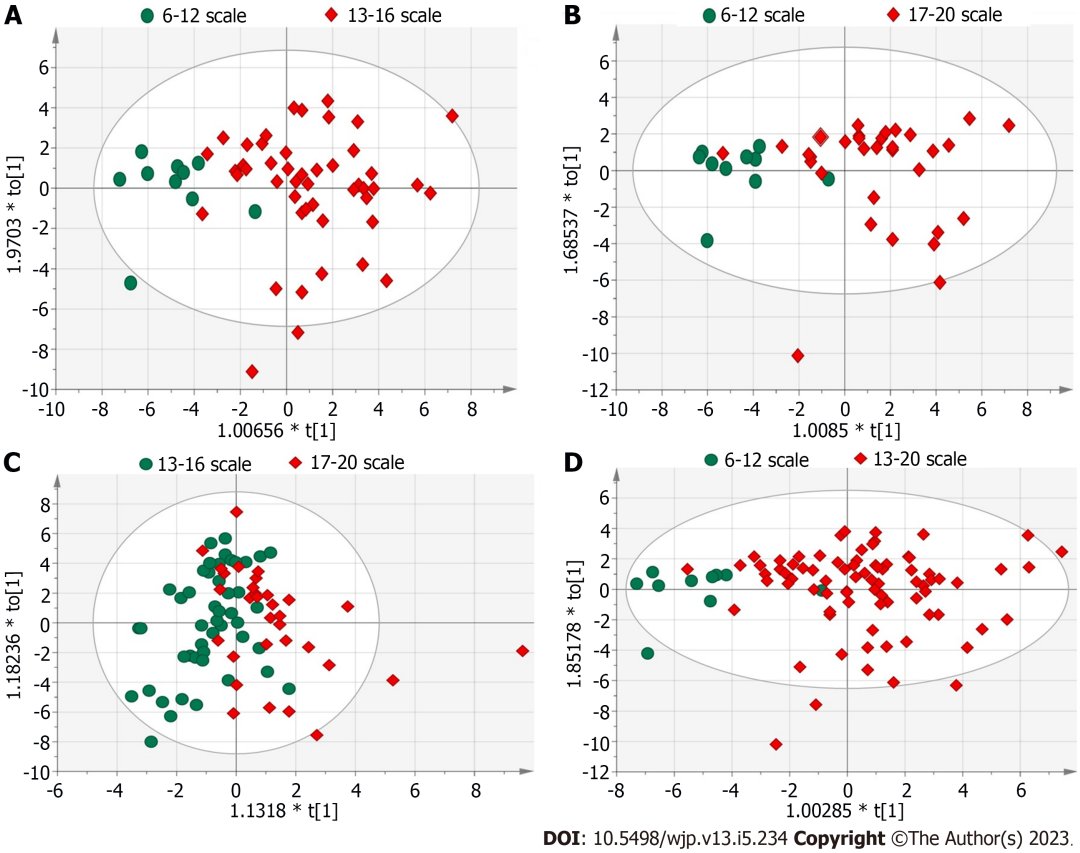
Figure 1 Changes in organic acids and myoglobin levels before and after exercise. A: Volcano maps before and after training; B: Statistical analysis of myoglobin levels before and after training.

supplying energy through aerobic metabolism in the body[27]. Aerobic metabolism has a long oxygen supply capacity and is an important pathway of energy metabolism[28]. Exercise-related fatigue after long and intense exercise is related to metabolic changes in TCA cycle[29]. High intensity training significantly increased the content of intermediates in the TCA cycle, Tsai *et al*[30] reported that succinic acid and fumaric acid were significantly elevated after exhaustion. In this study, we also observed higher levels of intermediate products of the TCA cycle in the higher BRPE scale group, which is consistent with previous studies mentioned above, suggesting fatigue occurrence in higher BRPE scale individuals. Interactions between the amino acid pool and the TCA cycle are suggested to play a central



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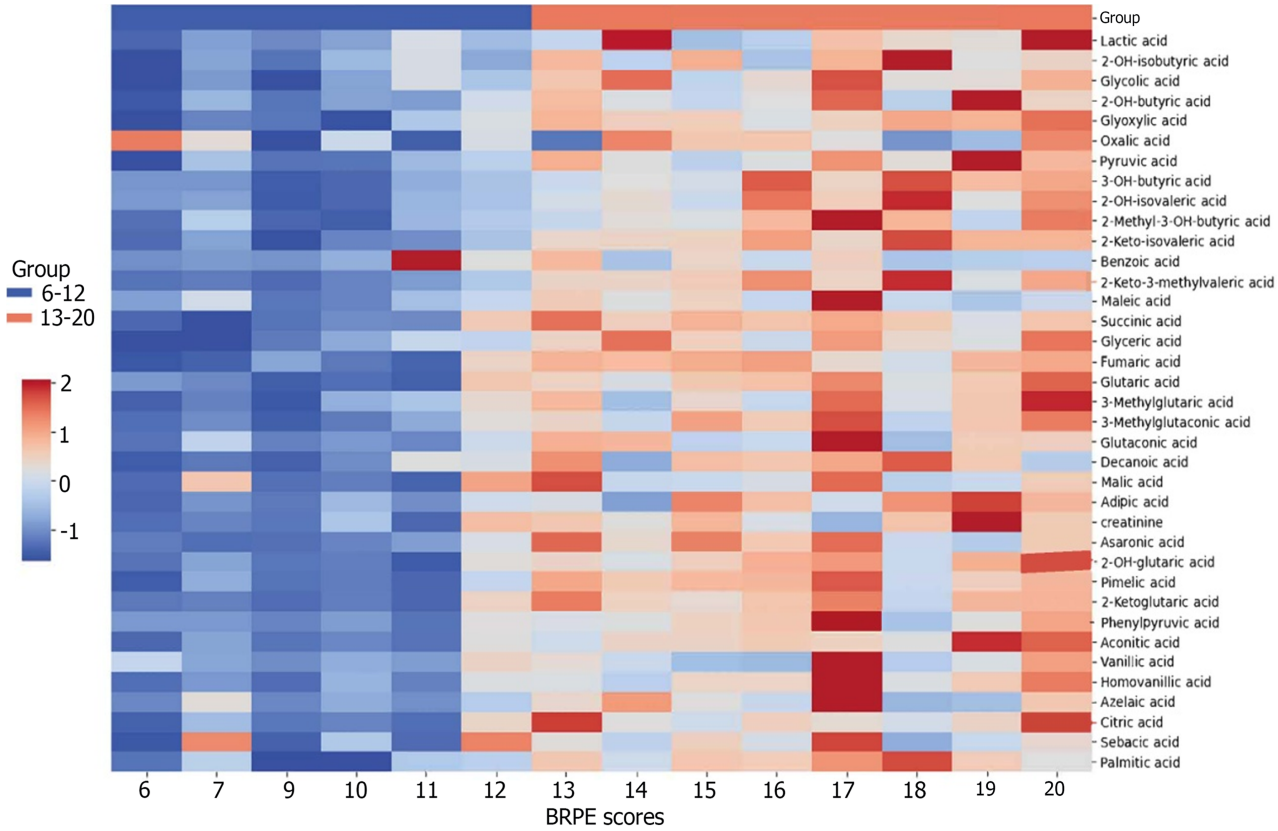
Figure 2 Principal component analysis scores of organic acid metabolites among the 6-12, 13-16 and 17-20 score groups.



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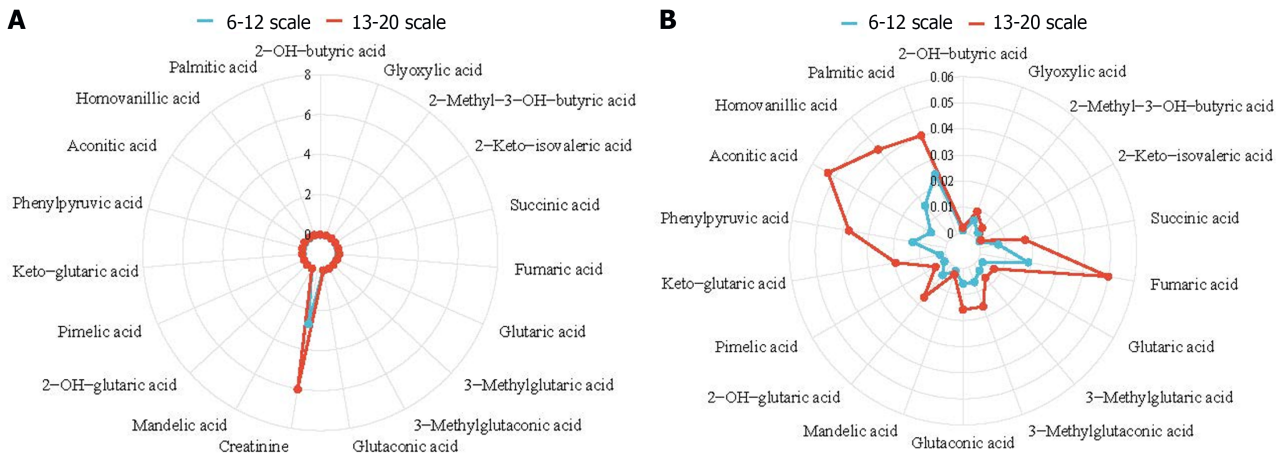
Figure 3 Orthogonal partial least-squares discrimination analysis of Borg's Rating of Perceived Exertion Scale and organic acid metabolism. A: Orthogonal partial least-squares discrimination analysis (OPLS-DA) between the groups with scores of 6-12 and 13-16; B: OPLS-DA between the groups with scores of 6-12 and 17-20; C: OPLS-DA between the groups with scores of 13-16 and 17-20; D: OPLS-DA between the groups with scores of 6-12 and 13-20.

role in the energy metabolism of the exercising muscle[31]. These results were consistent with the current "wear out doctrine" and "blockage doctrine" for the mechanism of training-induced fatigue; namely, the consumption of a large amount of energy substances and accumulation of metabolites during physical exercise/training leads to a decrease in the functional capacity of tissues, muscles, and organs, ultimately resulting in fatigue[1].



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Figure 4 Heatmap of Borg's rating of perceived exertion Scale and organic acid metabolites. BRPE: Borg's rating of perceived exertion.

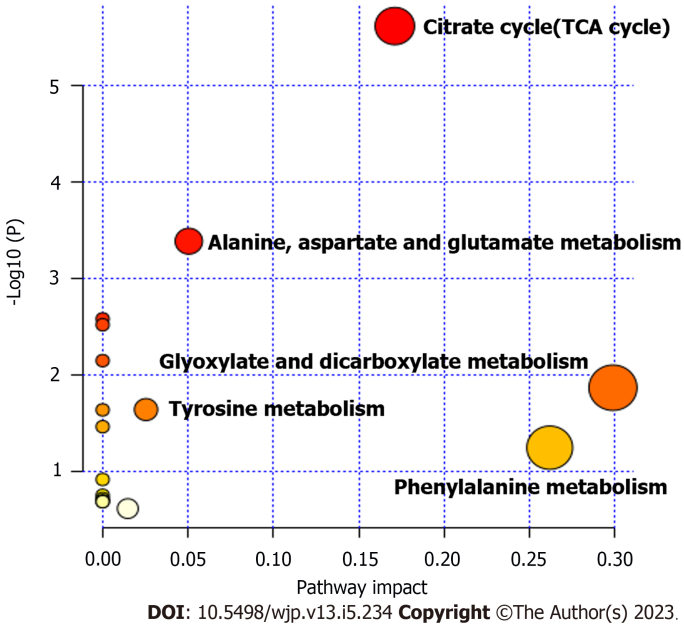


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Figure 5 Radar chart of the metabolism of different organic acids. A: Radar chart including creatinine; B: Radar chart excluding creatinine.

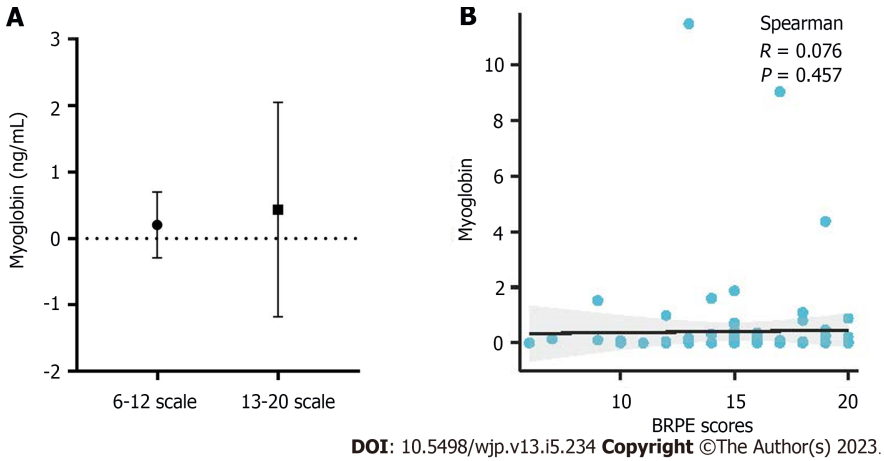
In addition, there was no significant difference between groups with scores of 6-12 and 13-20, and no correlation between myoglobin levels and BPRE scores. This result explains why serious muscle injury does not occur in the body even if a participant feels very tired psychologically during the 40 km exercise. However, at this time, organic acid metabolism has changed significantly and precedes the occurrence of muscle injury.

There are still some limitations in this research. First, the number of people in the group with a score of 6-12 was slightly small, which may have affected the data to a certain degree. Second, the population in this study only included men, and the difference between men and women was not assessed. Third, there was an absence of more direct assessment indicators, such as heart rate, blood biomarkers and others, which might be correlated with metabolic data. Combining all of these data might further help to confirm the ability of higher and lower BRPE values to differentiate metabolic profiles.



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Figure 6 Pathway analyses of different organic acid metabolites between the groups with Borg's rating of perceived exertion scores of 6-12 and 13-20. TCA: Tricarboxylic acid.



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Figure 7 Correlation analysis between Borg's rating of perceived exertion scale and myoglobin levels. A: Statistical analysis between the groups with scores of 6-12 and 13-20; B: Spearman's correlation analysis between the Borg's rating of perceived exertion scale and myoglobin levels. BRPE: Borg's rating of perceived exertion.

CONCLUSION

In conclusion, our results showed that after long-distance hiking with weight bearing, individuals with high BRPE values have a significant higher disturbance in organic acid metabolism. The differentially abundant metabolites are concentrated in the energy metabolism pathway. The BRPE value is not correlated with urine myoglobin levels but was shown to be able to discriminate individuals with exercise-related fatigue as a convenient predictor.

ARTICLE HIGHLIGHTS

Research background

The Borg's rating of perceived exertion (BRPE) scale was widely used to access subjective perception of effort during exercise, but the relationship between BRPE scale and urinary organic acids metabolism has not been studied.

Research motivation
Our article mainly explored the relationship of urinary organic acids metabolism and the BRPE scale during exercise and reflected the psychological perception degree of effort from an objective physiological perspective.

Research objectives
In this work, we aimed to evaluate whether the BRPE scale could be used in the prescription of outdoor hiking with weight-bearing based on urinary organic acids metabolism, which provides an objective physiological data support for the application of BRPE scale in outdoor hiking training.

Research methods
Eighty-nine healthy men participated in this project and underwent 40 km (6 h) training with 20 kg carriages. After the training, they truthfully filled in the BRPE scale and urinary organic acids were detected. We used multidimensional statistical analysis including principal component (PCA) analysis and orthogonal partial least-squares discrimination (OPLS-DA) analysis and heat map analysis to explore the differences in metabolic profiles of organic acids with different BRPE scale. At last, differential metabolites were screened and pathway analysis was performed.

Research results
There were significant statistical differences in urinary organic acids before and after exercise. According to the BRPE scale, individuals were divided into groups of 6-12 scale (easy), 13-16 scale (somewhat hard) and 17-20 scale (very hard). PCA results showed no separation trend among the three groups. Further analysis with OPLS-DA showed that, group of 6-12 scale and 13-16 scale, 6-12 scale and 17-20 scale could be separated obviously, and group of 13-16 scale and 17-20 scale could not be separated, so group of 13-16 scale and 17-20 scale were combined into group 13-20 scale. OPLS-DA results showed that group 6-12 scale and 13-20 scale could be separated. Heat map results also showed significant metabolic differences between group of 6-12 scale and 13-20 scale. According to the standard of a variable importance in the projection > 1, fold change > 1.5 and $P < 0.05$, 19 different metabolites were screened, which mainly in citrate cycle (tricarboxylic acid cycle) and alanine, aspartate and glucose metabolism.

Research conclusions
Our results showed that the BRPE scale could be used to monitor body fatigue in long-distance outdoor hiking with weight bearing.

Research perspectives
We provide an objective method to evaluate body fatigue in outdoor-hiking exercise.

FOOTNOTES

Author contributions: Sang PP and Zhang ML designed the study; Sang PP, Li J, Tan XD and Peng W performed the research; Sang PP and Zhou HH analyzed the data; Sang PP wrote the paper; and Tian YP and Zhang ML revised the manuscript for final submission.

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SYSTEMATIC REVIEWS

Knowledge, attitudes and experiences of genetic testing for autism spectrum disorders among caregivers, patients, and health providers: A systematic review

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Abstract

BACKGROUND

Several genetic testing techniques have been recommended as a first-tier diagnostic tool in clinical practice for diagnosing autism spectrum disorder (ASD). However, the actual usage rate varies dramatically. This is due to various reasons, including knowledge and attitudes of caregivers, patients, and health providers toward genetic testing. Several studies have therefore been conducted worldwide to investigate the knowledge, experiences, and attitudes toward genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers who provide medical services for them. However, no systematic review has been done.

AIM

To systematically review research on knowledge, experiences, and attitudes towards genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and searched the literature in three English language databases (PubMed, Web of Science, and PsychInfo) and two Chinese databases

(CNKI and Wanfang). Searched literature was screened independently by two reviewers and discussed when inconsistency existed. Information on characteristics of the study, characteristics of participants, and main findings regarding knowledge, experience, and attitudes of caregivers of children with ASD, adolescent and adult ASD patients, and health providers concerning ASD genetic testing were extracted from included papers into a charting form for analysis.

RESULTS

We included 30 studies published between 2012 and 2022 and conducted in 9 countries. Most of the studies (n = 29) investigated caregivers of children with ASD, one study also included adolescent and adult patients, and two covered health providers. Most (51.0%-100%) of the caregivers/patients knew there was a genetic cause for ASD and 17.0% to 78.1% were aware of ASD genetic testing. However, they lacked full understanding of genetic testing. They acquired relevant and necessary information from physicians, the internet, ASD organizations, and other caregivers. Between 9.1% to 72.7% of caregivers in different studies were referred for genetic testing, and between 17.4% to 61.7% actually obtained genetic testing. Most caregivers agreed there are potential benefits following genetic testing, including benefits for children, families, and others. However, two studies compared perceived pre-test and post-test benefits with conflicting findings. Caregivers concerns included high costs, unhelpful results, negative influences (*e.g.*, causing family conflicts, causing stress/risk/pain to children *etc.*) prevented some caregivers from using genetic testing. Nevertheless, 46.7% to 95.0% caregivers without previous genetic testing experience intended to obtain it in the future, and 50.5% to 59.6% of parents previously obtaining genetic testing would recommend it to other parents. In a single study of child and adolescent psychiatrists, 54.9% of respondents had ordered ASD genetic testing for their patients in the prior 12 mo, which was associated with greater knowledge of genetic testing.

CONCLUSION

Most caregivers are willing to learn about and use genetic testing. However, the review showed their current knowledge is limited and usage rates varied widely in different studies.

Key Words: Autism spectrum disorder; Genetic testing; caregivers; Child and adolescent psychiatrists; Knowledge; Experience; Attitudes

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Core Tip: More action should be taken to improve the knowledge level about genetic testing among caregivers of patients with autism spectrum disorder (ASD). Health education from health providers such as physicians and psychiatrists appear the most effective method. Improving the knowledge level of ASD genetic testing among health providers is necessary for better utilization of genetic testing in ASD practice. Caregivers of patients with ASD and patients themselves generally hold a positive attitude toward genetic testing. More comprehensive knowledge is needed to avoid potential misunderstandings.

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INTRODUCTION

Autism spectrum disorder (ASD) is a group of severe neurodevelopmental disorders currently with limited treatment effectiveness[1]. The prevalence of ASD is around 1% but has been steadily increasing over the past two decades[2]. Diagnosis of ASD lacks objective biomarkers and primarily relies on subjective parameters such as clinical observation and evaluation of individuals' behavioral and developmental characteristics[3]. However, most patients are too young to express their feelings, clinical symptoms are complex and heterogeneous, not easily detected by parents and many patients do not receive timely diagnosis and treatment. This can lead to severe social dysfunction and heavy economic burden to families and society[4-6]. Although the specific etiology of ASD is unknown, it is widely accepted that both genetic and environmental factors contribute to the pathogenesis of ASD. The estimated heritability of ASD ranges from 64% to 91%[7], and there are a large number of studies to

elucidate the genetic mechanism of this disorder. Thousands of ASD risk genes carrying different kinds of mutations have been reported, such as rare *de novo* mutations, single nucleotide polymorphisms (SNPs), and copy number variations (CNVs)[8-10]. There are several comprehensive databases that aim to summarize all ASD risk genes and SFARI Gene (gene.sfari.org)[11] is one of the most well-recognized. SFARI Gene features a ranking system that gives users an estimate of the strength of the evidence in favor of each gene. For example, there are 232 genes with high confidence, which means these genes have been clearly implicated in ASD. As a result, several genetic testing techniques have been applied as an auxiliary examination tool when diagnosing ASD.

In clinical practice, genetic testing, such as Karyotype analysis, fluorescence in-situ genomic hybridization (FISH), fragile X testing, chromosome microarray analysis (CMA), and next-generation sequencing have all been utilized for ASD patients. Karyotype analysis was first used in the 1970s to identify extremely large CNVs[12] and FISH has been performed to identify submicroscopic CNVs since the 1990s[13]. In 2005, the American College of Medical Genetics and Genomics (ACMG) recommended karyotype analysis and FISH as standard testing for children with developmental delay or mental retardation, which included ASD[13-15]. For ASD with specific genetic causation, genetic testing could be utilized as the first-tier diagnostic tool. For example, 30%-50% fragile X syndrome caused by > 200 repeats of the CGG motif in FMR1 was shown to manifest as ASD[16]. In 2007, the American Academy of Pediatrics recommended Fragile X testing to be performed when ASD was diagnosed[17-19]. Given that ASD is polygenic, screening mutations genome-wide is necessary. CMA that could detect CNVs and SNPs across the genome has been increasingly used in the clinical practice of ASD[20]. The latest next-generation sequencing with higher resolution, including Whole Exome Sequencing (WES) and Whole Genome Sequencing could be used to detect single nucleotide variants, indels and other variants in patients[21]. CMA and WES have been recommended as the first-tier clinical diagnostic test for individuals with developmental disabilities, including ASD by the ACMG in 2010 and 2013, respectively [12,22]. So far, the clinical diagnostic yield of CMA and WES for ASD was 9.3 to 24.1%[23], and 8.4% to 15.4%[24,25] respectively.

There are many potential benefits of genetic testing for patients with ASD and their families, including promoting early diagnosis and intervention, identifying etiology, reducing medication compliance, providing scientific suggestions for parents' fertility planning, and reducing parents' guilt and anxiety[26,27]. However, the usage rate of genetic testing varies dramatically across countries and regions. As far as we know, the highest rate of receiving any type of genetic testing was reported in France in 2014 (61.7%)[28]. Much lower rates were reported in America in 2020 (17.4%) and Malaysia in 2022 (19.8%)[29,30]. Even within the same country in the same year (for example, America in 2018), rates ranged from 28.0% to 57.1%[31,32]. This could be due to several factors. First, genetic testing does not always identify pathogenic variants because the complex genetic architecture of ASD is still not fully understood[33,34]. Second, a positive finding from genetic testing is not always helpful in clinical management. Third, the test is costly for some families[31]. Furthermore, the usage rate of genetic testing is affected by awareness and attitudes of both caregivers and health providers who are involved in the diagnosis and care of children with ASD, especially child and adolescent psychiatrists (CAP)[31, 35]. In a previous study, 67.5% of parents reported that the main reason why they did not get genetic testing was they did not receive suggestions from physician[36].

To maximize the benefit of genetic testing in ASD clinical practice, it is very important to understand caregivers' and health providers' opinions towards genetic testing for ASD. To date, several studies have investigated knowledge, experiences, and attitudes toward genetic testing for ASD. In the present article, we systematically reviewed the literature published up to October 2022 to outline the current state of knowledge level, experiences, and attitudes toward ASD genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers. In addition, to summarize factors related to the underutilization of genetic testing and provide a direction for future improvement.

MATERIALS AND METHODS

Literature search

We searched the literature in 3 English databases (PubMed, Web of Science, and PsychInfo) and 2 Chinese databases (CNKI and Wanfang). The search items were (caregivers* OR caretakers* OR parents * OR psychiatrist* OR specialists*) AND (autism spectrum disorder OR ASD* OR autism* OR autistic) AND (genetic testing OR genetic assessment OR genetic risk assessment) AND (knowledge* OR awareness* OR perception* OR attitudes* OR experiences* OR utilization* OR utility* OR interest*). The final search was done on October 7, 2022, and searched literature was exported to Endnote X9.

Inclusion and exclusion criteria

Peer-reviewed articles that met all the following criteria were included in our research: (1) The targeted disease was ASD; (2) participants were either caregivers of children with ASD, adolescent and/or adult ASD patients, or health providers who provided medical services for them; and (3) the article focused on evaluating the knowledge, experiences, or attitudes about ASD clinical genetic testing. Articles were

excluded if: (1) Participants other than the target population described above were included; (2) none of the three topics of interest was covered; (3) the study focused on prenatal genetic testing; (4) the article was not written in English or Chinese; (5) the study was a review; or (6) full-text was unavailable.

Selection of sources of evidence

We first screened the searched papers by reading titles and abstracts. Then, full texts of the remaining studies were read and those that met the eligibility criteria were included for further study. These two steps were carried out by two independent reviewers. When there was non-conformity, a discussion was organized, and a senior reviewer was invited if necessary. The whole process of selection was displayed in the PRISMA flowchart (Figure 1)[37].

Data charting process

Relevant information of included papers was extracted into a charting form, including: (1) Characteristics of the study (author affiliation, country, year of publication, time period(s) of the study, study setting, sample size, sampling method, survey methods, and tools); (2) characteristics of participants (age of child at diagnosis and at survey time, financial insurance of child, relationship with ASD patients, age, gender, marital status, educational level, annual income, current employment status, number of children, number of children with ASD, and family history of ASD); and (3) main findings of the study (knowledge, experience, and attitudes concerning ASD genetic testing). The details were displayed in supplementary materials. After reading all 30 included articles and discussing them, a coding instruction was summarized by two reviewers. The data were then extracted by one reviewer and checked by another reviewer.

RESULTS

Search results

The original search yielded 483 records. After removing duplications and screening abstracts, 78 remained for full-text screening, after which, 30 records were included. Reasons for exclusion were a. inclusion of subjects other than the target population, for example, caregivers of patients with developmental disorders other than ASD, such as intellectual disability, developmental disorder (n = 16), general population (n = 16); b. not covering any of the three topics of our interest (n = 5). The process of article selection is displayed in Figure 1.

Characteristics of studies

Among the final included 30 studies, 20 (66.7%) investigated knowledge, 17 (56.7%) investigated experience, and 22 (73.3%) investigated attitudes toward ASD genetic testing. They were published between 2012 and 2022, and conducted in 9 countries, with 19 (63.3%) in United States. More than half (n = 17, 56.7%) utilized convenience sampling. Other sampling methods included purposive sampling (n = 6, 20.0%), random sampling (n = 3, 10.0%), and snowballing sampling (n = 3, 10.0%). Investigating methods included online surveys (n = 16, 53.3%), face-to-face interviews (n = 9, 30.0%), and telephone calls (n = 7, 23.3%). The most frequently used instrument was a questionnaire with open-ended questions (n = 14, 46.7%). Some instruments included both close-ended and open-ended questions (n = 7, 23.3%), or only close-ended questionnaires (n = 7, 23.3%). More details can be found in Table 1. A standard questionnaire which was defined as a questionnaire with focused themes and standard evaluating methods and could be utilized by other researchers with a similar research purpose was used in two studies—Perceptions of ASD Genetic Testing Survey developed by Zhao *et al*[38] and The Centers for Autism and Related Disabilities developed by Cuccaro *et al*[39].

Characteristics of participants

The majority of the studies (n = 29, 96.7%) investigated parents of children with ASD, including 23 (75.9%) that only covered parents, 4 (13.8%) that also covered other caregivers[27-29,31], one also included health providers[32], and 1 (3.4%) that included adolescent and adult patients[40]. Only one study investigated CAP alone[41]. The sample size of the 30 included studies ranging from 20 to 1444. Of 19 studies that provided gender information, 60%[35] to 95%[42] of the participants were female. Of 13 studies that reported the mean age of parents, these ranged from 37.4[36] to 46.7[43]. Of 8 studies that reported the marital status of parents, 81.3%[44] to 92.3%[45] were married or living as married. Of 8 studies that investigated current employment status, 51%-71.1% of caregivers were employed. Of 16 studies that provided information about the educational level of caregivers, 21.0%-69.4% had a college or higher degree. The lowest educational level of parents was reported in 2 studies that only involved parents of children with ASD who had taken CMA testing[46,47].

Age information of children with ASD was provided in some studies, including 7 (24.1%) that reported mean current age ranging from 5.2 to 16.5 years old[26,43] and 5 (16.7%) that reported mean age at diagnosis ranging from 3.0[29] to 4.7[48] years old. Among 7 studies that reported the number of

Table 1 Characteristics of included studies

	Percentage	Raw count
Year of publication		
2012-2015	26.7%	8
2016-2019	43.3%	13
2020-2022	30.0%	9
Research country		
America	63.3%	19
Taiwan	13.3%	4
Europe	13.3%	4
Other (Canada, Jordan, Malaysia)	10.0%	3
Sampling method		
Convenience sampling	56.7%	17
Purposive sampling	20.0%	6
Random sampling	10.0%	3
Snowball sampling	10.0%	3
Missing	3.3%	1
Study setting		
Online	53.3%	16
Face to Face	30.0%	9
Telephone	23.3%	7
Missing	10.0%	3
Assessment tools		
Open-ended questionnaire	46.7%	14
Close and open-ended questionnaire	23.3%	7
Close-ended questionnaire	23.3%	7
Standard questionnaire	6.7%	2

children with ASD, most families (17.8%-93.7%) had only one child with ASD, while 5.9%-17.9% of families had two or more children diagnosed with ASD. Of 7 studies that addressed family history, 10.5%-34.6% of participants had a positive family history of ASD.

Knowledge, experiences, and attitudes

Specific questions related to the three topics of interest were (1) Knowledge: perceived cause(s) of ASD, knowledge about genetics and genetic testing, pathways to acquire such knowledge, and information needs prior to genetic testing; (2) Experience: experience of being referred to genetic testing and using genetic testing; and (3) Attitudes: why participants supported genetic testing and their concerns about genetic testing; for participants who have not done genetic testing, their intention to pursue genetic testing in the future; for participants who had done genetic testing, their satisfaction with ASD genetic testing and willingness to recommend genetic testing to others (Table 2).

Knowledge of genetics and ASD clinical genetic testing among parents and other caregivers: In total, there were 7 studies that surveyed the perceived cause(s) of ASD of the parents and other caregivers. These studies found that 51.0%-100% of the them thought ASD was partly or fully explained by genetic factors, and 11.9%-12.0% thought ASD was entirely explained by genetic factors. Parents who believed that their child's ASD was permanent tended to attribute ASD to genetic factors[16]. One study reported parents' understanding of genetics: parents stated that they were familiar with and knew the meaning of DNA (94%), genes (92%), chromosomes (86%), genetic testing (87%), and CMA (21%)[39].

In addition, there were 14 studies that investigated caregivers' knowledge of genetic testing for ASD. Of seven studies that asked them whether they were aware of ASD genetic testing before the study, 17.0% to 78.1% answered yes[29,49-54]. However, one study reported that 95% of the participants said

Table 2 The topics covered by 30 included studies

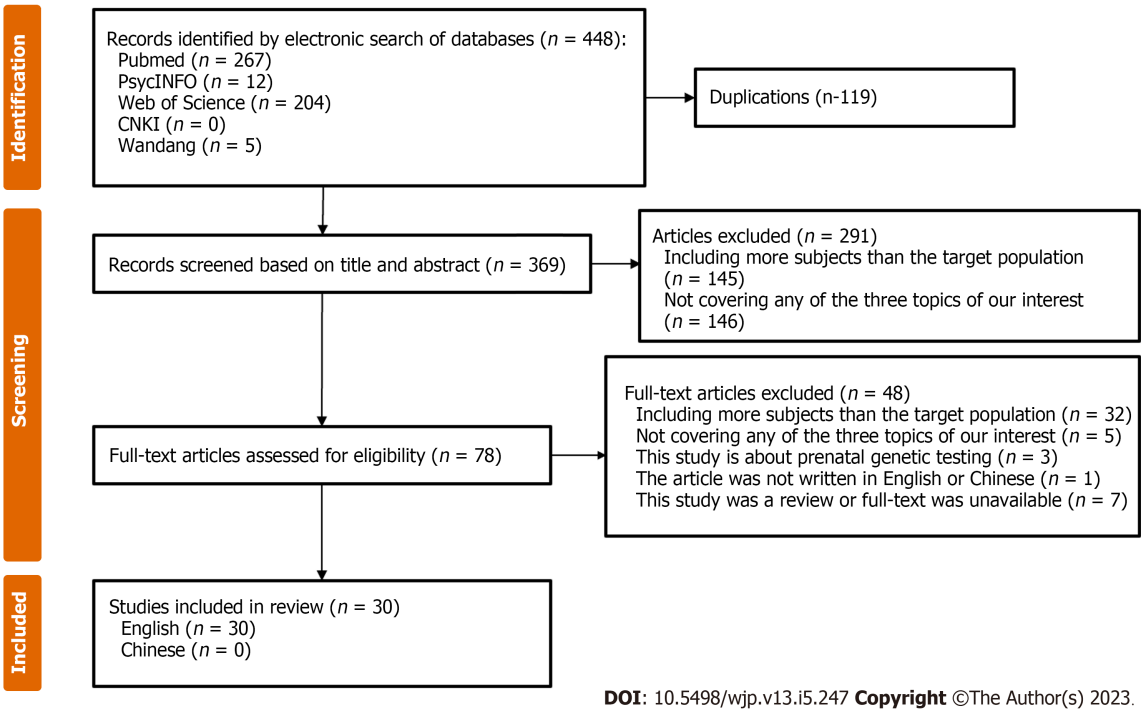
ID	Year	Country/Region	Main findings										Ref.
			Knowledge				Experience		Attitude				
			Cause (s) of ASD	Genetics and genetic testing	Pathway to acquire knowledge	Information needed	Being referred	Using	Perceived benefits	Perceived concerns	Intention to pursue	Intention to recommend	
1	2012	America						a		a			[55]
2	2013	America	a					a	a		a		[45]
3	2013	America		a	a				a	a	a		[51]
4	2014	America	a	a			a	a	a				[36]
5	2014	America, France	a					a					[25]
6	2014	Taiwan	a										[42]
7	2015	America							a				[43]
8	2015	America								a			[41]
9	2016	America		a					a	a			[32]
10	2016	America		a		a		a					[50]
11	2016	America, Canada	a										[39]
12	2017	Norway							a	a			[40]
13	2017	Spain					a	a	a	a	a		[53]
14	2017	America	a										[44]
15	2018	America	a	a					a	a			[23]
16	2018	America					a	a	a	a	a		[28]
17	2018	America					a	a					[29]
18	2019	America		a	a			a	a	a		a	[46]
19	2019	Taiwan		a	a								[47]
20	2019	America		a	a	a							[52]
21	2020	America		a			a	a	a	a	a		[26]
22	2021	America		a							a		[54]
23	2021	America						a	a				[38]

24	2021	America						a	a				[35]
25	2021	Taiwan	a					a	a	a			[48]
26	2022	Sweden	a			a		a	a		a		[37]
27	2022	Taiwan	a							a			[49]
28	2022	America					a	a					[24]
29	2022	Jordan					a		a				[33]
30	2022	Malaysia	a				a		a				[27]

they did not know what genetic tests can test[26]. Furthermore, in one study of participants without genetic testing experience conducted in Sweden in 2020, only 16.2% of parents and 19.6% of autistic adolescents and adults believed that genetic testing for ASD was available[40]. There were three studies from the same team using the same seven-item questionnaire about knowledge of ASD genetic testing. In this questionnaire, wrong and correct answers were scored 0 and 1, with a total score ranging from 0 to 7. The three studies were all performed among parents with children with ASD from United States in 2019. The mean score for those studies were 2.4 ± 1.2 (n = 411), 2.5 ± 1.2 (n = 552), and 2.5 ± 1.2 (n = 443), respectively[18,24,26]. Caregivers' knowledge of ASD genetic testing was positively associated with their educational level, the number of children with ASD, and socioeconomic status, and negatively related to the severity of the child's ASD diagnosis[52,54,55]. Furthermore, caregivers who had visited a genetic service and who had received information from physicians rather than other sources also had a higher level of knowledge[55,56].

In 4 studies that reported the pathways through which the parents had acquired knowledge about ASD genetic testing, 18.3%-57.7% of the participants received related information from physicians[49,50,54,55]. Other main resources include the internet or mass media (23.9%-45.7%)[50,54,55], ASD organization or support groups (12.0%-42.9%)[50,54,55], and other parents of children with ASD (17.0%-36.4%)[50,54,55]. Two studies reported what information parents wanted to know to improve their knowledge about genetic testing. This information included: accuracy of genetic testing (38% and 88.4%), cost (60.0% and 85.9%), benefits of genetic testing (48.0% and 83.8%), testing procedure (29.0% and 77.8%), eligibility to undergo genetic testing (62.4%), potential harms caused by genetic testing (29.0% and 56.1%), previous use and experience among individuals affected by ASD (50.8%), and confidentiality issues (12.0% and 48.0%)[53,55].

Experiences of ASD clinical genetic testing: Parents and other caregivers: Three (10.0%) of the 30 studies only included parents of children with ASD who had undergone CMA testing, and one only included parents who had been offered any genetic testing for their child with ASD. Among the remaining studies, 6 reported that 9.1% to 72.7% of caregivers and 2.8% of autistic adolescents/adults [40] had been referred to genetic testing, and 13 (43.3%) studies reported rates of using any type of genetic testing ranging from 17.4% in United States[29] to 61.7% in France[28]. Regarding specific types of genetic testing, fragile X testing was most widely used by parents, with utilization rates ranging from 4.4% to 39.2%[36,39,49,56]. The utilization rates of CMA and karyotype tests were 7.4%-13.1%[49,56],



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Figure 1 PRISMA flowchart.

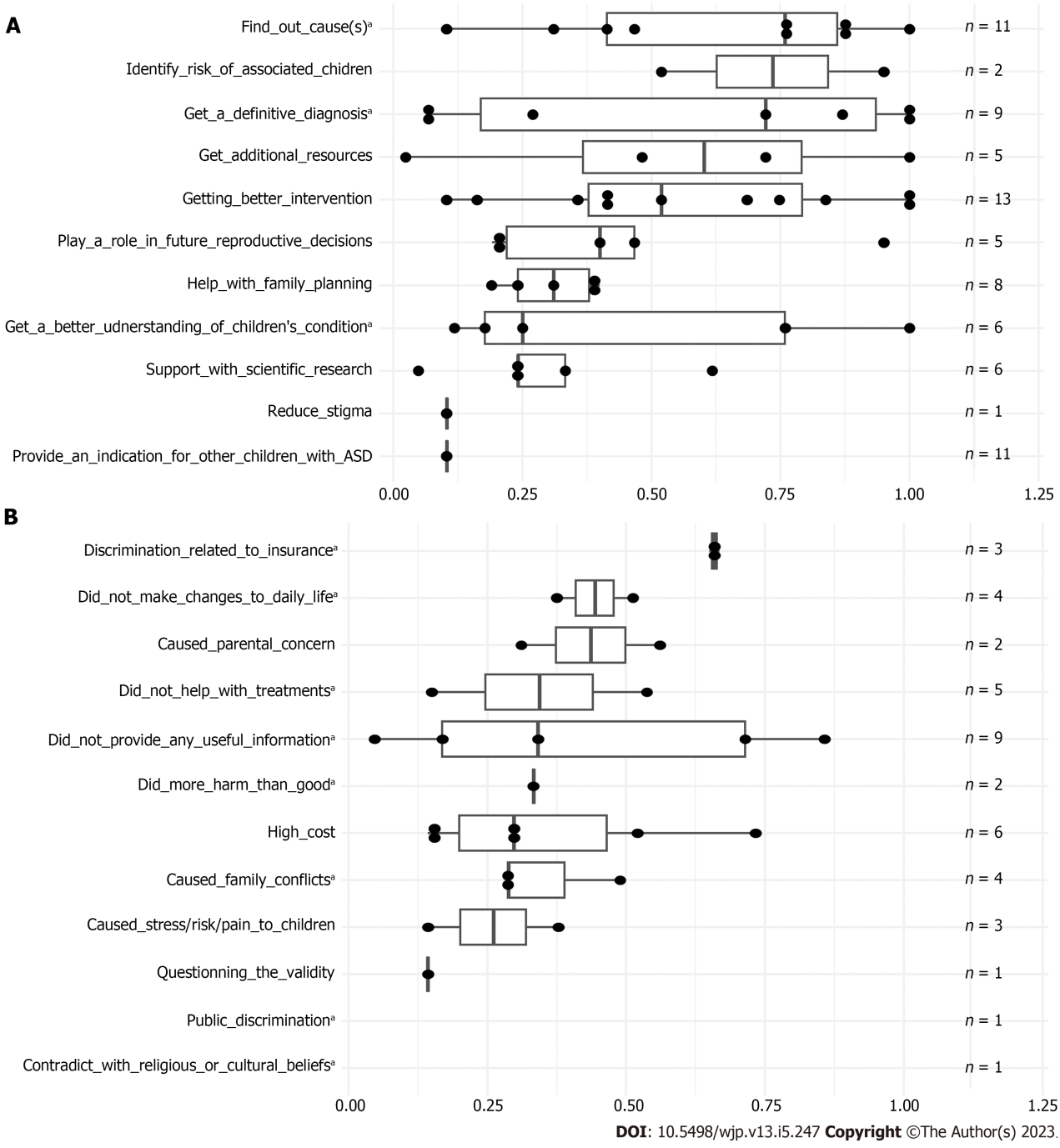
and 0.7%-37.6%[36,49,56], respectively. Only one study in Jordan reported that the usage rate of WES was 3.3%[36]. The associated factors of caregivers' usage of genetic testing were reported in 4 studies. Those who had a higher awareness level of genetic testing[49], who received related information from healthcare providers rather than other sources[31,49], who had visited geneticists[31,56], and those with higher household income[36] were more likely to conduct genetic testing for their child.

Health providers: Only one study was of CAP and was performed in United States in 2021. It showed that 54.9% of respondents had ordered ASD genetic testing for their patients in the prior 12 mo. Psychiatrists who accepted a higher percentage of ASD cases, who had more knowledge about genetic testing and higher perceived utility of ASD genetic testing, and who were at a University medical center were more likely to request genetic testing for their patients with ASD; participants with more years of working experience tended not to order genetic testing for their patients with ASD[41].

Attitudes towards ASD clinical genetic testing: Parents and other caregivers: There were 15 surveys among caregivers which reported participants' reasons for supporting genetic testing. Reasons could be categorized into three groups: (1) Benefits for the child, including getting better intervention (n = 13), finding out the cause(s) of ASD (n = 11), getting a definitive diagnosis (n = 8), getting a better understanding of their condition (n = 6), and additional resources (n = 5); (2) Benefits for family and parents, including helping with family planning (n = 8), and future reproductive decisions (n = 5), identifying risk of associated children (n = 2), and reducing stigma (n = 1); and (3) Benefits for other people, including promoting scientific research (n = 6), and providing an indication for other children with ASD (n = 1) (Figure 2A).

Of caregivers who had taken their child for genetic testing, more than half held positive attitudes toward their experience of genetic testing, reporting that genetic testing had been helpful for their child and their family[29,46,49]. Getting additional resources (81.8%), getting a definitive diagnosis (81.8%), contributing to scientific knowledge (61.8%), identifying associated medical risks (25.0%), playing a role in future reproductive decisions (19.1%), helping with treatment planning (12.5%, 16.2%, 90.9%), gaining a better understanding of the child (10.3%), finding a cause of ASD (10.3%, 12.5%), and helping with family planning were reasons why they thought genetic testing was useful[29,31,46,49]. Two studies compared perceived benefits between caregivers, one who had taken their children for genetic testing and the other who never had. The first showed that the post-test group had more positive attitudes toward ASD genetic testing[31], the second reported less positive attitudes[27].

There were 15 studies that reported caregivers' concerns about genetic testing. They can be divided into four areas: (1) High cost (n = 6); (2) useless results: Would not provide any useful information (n = 9), would not help with treatments (n = 5), and would not make changes to daily life (n = 4); (3) negative influences: Would cause family conflicts (n = 4), would cause stress/risk/pain to children (n = 3), cause parental concern (n = 2), would do more harm than good (n = 2), and contradict their religious or cultural beliefs (n = 1); would cause discrimination when buying financial insurance (n = 3) and public



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Figure 2 The support rates of potential benefits and concerns of autism spectrum disorder genetic testing. A. Potential benefits of autism spectrum disorder (ASD) genetic testing; B. Potential concerns about ASD genetic testing. Each dot represents a study and the total number of studies that report the corresponding benefit/concern is displayed on the right side of the figure. Benefits/concerns were sorted by the median of the reported support rate of the participants. [a]indicates that there are studies that only report a qualitative description.

discrimination (n = 1); and (4) other: The test had poor validity (n = 1) (Figure 2B). Four studies reported concerns of participants who had taken their child to genetic testing: lack of detailed information and did not help with further treatment and financial costs were the main reasons for dissatisfaction[26,40,44,49]. Parents' attitudes towards genetic testing were positively related to their perceived severity of ASD[57] and negatively related to their perceived barriers in conducting genetic testing[57], and parents' age and educational level[52].

There were 8 (26.7%) studies which reported that 46.7%[54] to 95%[56] of caregivers without previous genetic testing experience intended to pursue genetic testing in the future, and 2 studies showed that 50.5% and 59.6% parents who have purchased genetic testing services for their children would recommend genetic testing to other parents. It is reported that parents' willingness to pursue genetic testing for their children with ASD was positively associated with their attitudes towards genetic testing, their perception of other people's opinions, and their self-efficacy in pursuing genetic testing

[57].

Health provides: Only one survey among CAP reported why they order genetic testing for their patients. The main reason is to diagnose ASD and reported by 59.9% of those who had ordered a genetic testing in the prior 12 mo[41].

DISCUSSION

To the best of our knowledge, this is the first study that systematically reviewed caregivers', patients', and health providers' knowledge, experiences, and attitudes toward genetic testing for ASD. We searched the related literature without area and time limitations, extracted, and analyzed information from 30 studies. We found that most caregivers agreed that genetic mutations are causes of ASD and knew a little about ASD genetic testing but lacked a deeper understanding of the tests. Caregivers can obtain information about ASD genetic testing from several sources, including physicians, the internet, ASD organizations, and other caregivers of ASD patients. Most obtained information from non-professionals, although obtaining information from professionals contributes to better knowledge and more willingness to use ASD genetic testing. The usage rate of ASD genetic testing is generally low and varied dramatically among studies, even within the same country in the same year, as did the rate of being referred for ASD genetic testing by health providers. In addition, caregivers generally held positive attitudes toward genetic testing. More than half of the parents who had used genetic testing would recommend it to other parents and 46.7% to 95% of caregivers without previous genetic testing experience intended to pursue genetic testing in the future.

Although it is repeatedly reported that awareness level of genetic testing was closely associated with its usage rate and users' attitudes[41,49,56,58]. the awareness level of ASD genetic testing among both caregivers and health providers was not ideal. Most caregivers had heard a little about genetic testing, but few of them had a deep understanding. For example, less than 5% knew the diagnosis rate/yield of ASD genetic testing and the legitimate rights of children with ASD[57]. In contrast, over half of participants showed an interest in gaining more knowledge about genetic testing[55]. This indicates that caregivers generally have limited access to such knowledge. Given that a variety of methods to obtain relevant knowledge have been reported, the problem of the low knowledge levels among caregivers can easily be resolved if appropriate actions are taken.

Health providers, such as physicians and psychiatrists are key to improving the knowledge level of caregivers about ASD genetic testing because parents who acquire genetic information from them were more likely to agree to genetic testing[27,46]. However, most parents did not receive such knowledge from their health providers. For example, one study reported that only 35.3% of parents who were aware of genetic testing received information from their physicians[55]. In addition, another study, not included in our review, reported that more than half of caregivers had not received any additional information about ASD from their physicians following diagnosis, let alone knowledge about genetic testing[59]. This may be linked to lack of knowledge about screening and diagnosis of children with ASD among physicians[60]. A previous study reported that about half of pediatricians who had cared for children with ASD did not know the clinical guideline regarding genetic testing for children with ASD[61]. It is possible and of concern that physicians who know related guidelines may not comply with them. This could result in even lower usage rate of genetic testing[62]. Not receiving doctors' recommendations was also an important reason why ASD genetic testing usage rate was low[46]. Only 18% of physicians would recommend genetic testing to all children with ASD[61]. Physicians should be encouraged to learn more about genetic testing. They can also recommend genetic counseling to patients, which could help to increase parents' awareness level about genetic testing[30].

Although genetic testing is more widely approved and prices are decreasing, the usage rate has not recently increased. For example, in United States, the usage rate was 17.4% in a survey conducted in 2018, whilst four years earlier the rate was 57.1%[29,32]. The usage rate of 57.1% was reported in a survey in Washington[32]. As the capital of the United States, Washington is economically more developed than other regions in America, which contributes to a higher usage rate. The usage rate differed dramatically among different areas. The usage rate of any type of genetic testing was 19.8% in Malaysia in 2022, which was much lower than that in Spain in 2017 (51.0%) and in France in 2012 (61.7%)[28,30,56]. This might be caused by different level of economic development. Also, a study reported large difference in usage rate of genetic testing between America and France, with 27.8% in America and 61.7% in France[28]. The free access to care in France may be associated with higher compliance with genetic testing recommendations[28].

Although most caregivers agreed with the benefits of ASD genetic testing and expressed positive attitudes towards future testing, many concerns still exist which prevent them from seeking genetic testing. The most frequently reported concern was that they thought genetic testing would not provide any useful information for them and could not help with further treatment. This was also an important explanation for why they were unsatisfied with genetic testing[44]. Parents may hold high expectations, hoping test results bring a definitive diagnosis and etiology of ASD[44,49]. However, only 35% of ASD cases had genetic abnormalities, and about 80% of cases received negative results from CMA testing[25,

46]. Visiting genetic counselors should also be encouraged before and after testing to help caregivers make an informed decision, understand, and use testing results more wisely[63]. Besides, the high cost of genetic testing and lack of insurance were also important reasons why genetic testing was underutilized. A study in Jordan indicated that 72% of families reported overall costs of CMA and fragile X testing constituted over 30% of their annual income, and lack of testing resources and insurance coverage further increased the financial burden[36]. However, in the long term, genetic testing may promote an earlier diagnosis and improve the prognosis of children with ASD, consequently, saving future costs[25]. Governments are therefore encouraged to offer affordable genetic testing. For example, government-funded CMA tests are freely available for children diagnosed with ASD in Israel[25]. However, genetic testing results can cause negative emotions for parents and children. For example, some parents believed that they would be blamed or discriminated against if the ASD was verified as inherited from one of them[51], the testing procedure, especially blood draws, would make their child uncomfortable, and the stigma attached to mental illness would increase their level of stress[43,52]. Genetic counseling before and after testing is therefore necessary to minimize misunderstanding about genetic causes and psychological or marriage counseling may need to be considered to alleviate negative emotions.

There were some limitations in this systematic review. Firstly, published research was limited and mainly concentrated in United States and other developed countries. Understanding implementation of ASD genetic testing in low and middle-income countries could not be achieved from this review. Secondly, only two studies targeted health providers. Because it is one of the most effective ways to impart knowledge about genetic testing to caregivers, it is very important to understand both health providers' understanding and attitudes toward genetic testing. Furthermore, there was little uniformity in instruments used in studies lack uniformity making it difficult to synthesize and compare results.

Clinical implications

Firstly, more actions should be taken to improve the knowledge level of genetic testing among caregivers of patients with ASD. Health education through health providers, like physicians and psychiatrists, is the most effective way. Secondly, improving the knowledge of genetic testing among health providers is necessary for better utilization of genetic testing in ASD practice. Thirdly, caregivers of patients with ASD and patients themselves generally hold a positive attitude toward genetic testing. More comprehensive knowledge is needed to avoid potential misunderstandings.

CONCLUSION

The usage rate varied widely in different studies. It is mainly affected by the knowledge level of related parties. However, the review showed that although most caregivers are willing to learn about and use genetic testing, their current knowledge is limited.

ARTICLE HIGHLIGHTS

Research background

The popularity of genetic testing for patients with autism spectrum disorder (ASD) varies dramatically across countries. It is highly dependent on the knowledge, experiences, and attitudes toward genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers. As a result, many related studies have been conducted worldwide but no systematic review has been done.

Research motivation

Getting a better knowledge of factors that are associated with the usage rate of genetic testing for patients with ASD has the potential to maximize the benefits of the test for patients.

Research objectives

To systematically review research on knowledge, experiences, and attitudes towards genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers.

Research methods

We conducted a systematic review by searching the related literature without area and time limitations in both English language and Chinese language databases.

Research results

In 30 studies conducted in 9 countries,17.0% to 78.1% of caregivers/patients were aware of ASD genetic

testing. However, they lacked a full understanding of it. Between 9.1% and 72.7% of caregivers in different studies were referred for genetic testing, and between 17.4% and 61.7% actually obtained genetic testing. Among caregivers, 46.7% to 95.0% without previous genetic testing experience intended to obtain it in the future, and 50.5% to 59.6% of parents who previously obtained genetic testing would recommend it to other parents. In a single study of child and adolescent psychiatrists, 54.9% of respondents had ordered ASD genetic testing for their patients in the prior 12 mo.

Research conclusions

The usage rate varied widely in different studies. It is mainly affected by the knowledge level of related parties. However, the review showed that although most caregivers are willing to learn about and use genetic testing, their current knowledge is limited.

Research perspectives

Firstly, more actions should be taken to improve the knowledge level of genetic testing among caregivers of patients with ASD. Health education through health providers, like physicians and psychiatrists, is the most effective way. Secondly, improving the knowledge of genetic testing among health providers is necessary for better utilization of genetic testing in ASD practice. Thirdly, caregivers of patients with ASD and patients themselves generally hold a positive attitude toward genetic testing. More comprehensive knowledge is needed to avoid potential misunderstandings.

FOOTNOTES

Author contributions: Zhou M and Zhang YM contributes equally to this paper. Zhang YM and Zhou M provide the conceptualization; Zhang YM and Zhou M contributed to the methodology, literature searching, data extraction; Li T contributed to the administration resources, and supervision; Zhou M contributed to writing the original draft; Zhang YM and Li T contributed to reviewing the draft; all authors have read and approved the final manuscript.

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OPINION REVIEW

Pharmacotherapy in autism spectrum disorders, including promising older drugs warranting trials

Jessica Hellings

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Abstract

Available pharmacotherapies for autism spectrum disorders (ASD) are reviewed based on clinical and research experience, highlighting some older drugs with emerging evidence. Several medications show efficacy in ASD, though controlled studies in ASD are largely lacking. Only risperidone and aripiprazole have Federal Drug Administration approval in the United States. Methylphenidate (MPH) studies showed lower efficacy and tolerability for attention deficit hyperactivity disorder (ADHD) than in the typically developing (TD) population; atomoxetine demonstrated lower efficacy but comparable tolerability to TD outcomes. Guanfacine improved hyperactivity in ASD comparably to TD. Dextroamphetamine promises greater efficacy than MPH in ASD. ADHD medications reduce impulsive aggression in youth, and may also be key for this in adults. Controlled trials of the selective serotonin reuptake inhibitors citalopram and fluoxetine demonstrated poor tolerability and lack of efficacy for repetitive behaviors. Trials of antiseizure medications in ASD remain inconclusive, however clinical trials may be warranted in severely disabled individuals showing bizarre behaviors. No identified drugs treat ASD core symptoms; oxytocin lacked efficacy. Amitriptyline and loxapine however, show promise. Loxapine at 5-10 mg daily resembled an atypical antipsychotic in positron emission tomography studies, but may be weight-sparing. Amitriptyline at approximately 1 mg/kg/day used cautiously, shows efficacy for sleep, anxiety, impulsivity and ADHD, repetitive behaviors, and enuresis. Both drugs have promising neurotrophic properties.

Key Words: Autism; Pharmacotherapy; Dextroamphetamine; Loxapine; Amitriptyline; Minimally verbal; Neurotrophic

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Core Tip: Most prescribing in autism spectrum disorders (ASD) is off-label; only risperidone and aripiprazole are Federal Drug Administration-approved in ASD, for irritability. Atypical antipsychotics are associated with metabolic side effects. Loxapine at 5-10 mg/day resembled an atypical antipsychotic in positron emission tomography studies; preliminary studies and clinical experience in ASD suggest efficacy and a promising metabolic profile. Controlled attention deficit hyperactivity disorder (ADHD) medication trials in ASD youth include methylphenidate, atomoxetine and guanfacine. The author recommends dextroamphetamine as an important treatment option for ADHD in ASD. Amitriptyline often improves impulsive aggression, self-injury, sleep, anxiety and enuresis. This article recommends additional older drug trials in ASD: Detroamphetamine, amitriptyline, loxapine, and lamotrigine for likely seizures.

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INTRODUCTION

Autism spectrum disorder (ASD) is diagnosed using criteria of significant deficits in social communication and interaction, together with at least two types of restricted and repetitive interests and behaviors (RRBs)[1]. ASD develops prenatally and during early childhood. There is no longer an age cut-off for diagnosis, though it is often evident by age 1-3 years. The prevalence of ASD has risen globally since 2000. Two separate United States studies using the 2016 National Survey of Children's Health reported ASD prevalence of 1 in 40 children[2,3]. After decades there is still no definitive medication treatment for the core features of autism likely due to the heterogeneity of ASD, including various genetic causes. Recent studies with negative findings for core symptoms include oxytocin, bumetanide and selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram for RRBs[4]. A meta-analysis confirmed there are still no treatments with efficacy for RRBs[5].

In addition to core ASD disabilities, the majority of these individuals have other serious challenges affecting them. Approximately 30%-50% also have intellectual disability (ID)[6]. Those more severely affected for example by birth injuries may have hydrocephalus and cerebral palsy, along with varying degrees of motor paralysis. Although there is a tendency worldwide to diagnose ASD in high-functioning, milder cases, an estimated quarter of individuals with ASD have less than 20 words of expressive language and are thus minimally verbal[7]. Approximately 20%-40% of those with ASD also have epilepsy, with greater rates in the more severely affected[8], which includes minimally verbal individuals.

In addition, psychiatric illness occurs several times more commonly in those with ASD than in the general population[9,10]. Common presenting problems include hyperactivity, impulsive aggression, property destruction and self-injury, which are not Diagnostic and Statistical Manual-fifth edition-Text Revised (DSM-5-TR) diagnoses. A study of 1380 youth with ASD found that over two thirds (68%) manifested aggression towards a caregiver, and almost half (49%) showed aggression towards non-caregivers[11]. Psychiatrist training in the field of developmental disabilities is seriously lacking in most universities worldwide, and has marginally improved in the United States in the past 5 years[12,13]. Individuals with ASD and their caregivers have great difficulty identifying a provider in their geographical area who will treat them. The field still suffers from a serious lack of clinical trials to guide treatment of psychiatric comorbidity. Those providers who treat such patients must rely on the few ASD clinical trials published, experience gained by different medication trials, and extrapolation from studies in typically developing (TD) individuals.

An analysis of 33565 children with ASD, found that 35% received 2 or more psychotropic medications, while 15% received 3 or more[14]. Polypharmacy especially with antipsychotics is even greater in adults, when many non-psychiatric medications are also prescribed apart from psychotropic medications[15]. The lack of evidence base results inevitably in exposure of these individuals to repeated medication trials, an unnecessary burden of side effects, and attrition from care[16]. Individuals with ASD often have one or more comorbid DSM-5-TR diagnoses. Working DSM-5-TR diagnoses are important guides for selecting classes of medications. Diagnostic symptoms of DSM-5-TR diagnoses may be more difficult to recognize in those more severely affected, including the minimally verbal. The Diagnostic Manual of Intellectual Disabilities-2 (DM-ID2)[17] is a useful crosswalk for applying DSM-5 criteria to individuals with intellectual and developmental disorders and/or ASD. Clearly the verbal criteria for diagnoses are not used in the minimally verbal.

Only risperidone and aripiprazole are Federal Drug Administration (FDA)-approved in the United States for individuals with ASD and irritability. The few other drugs prospectively studied in

randomized controlled trials (RCTs) in ASD include methylphenidate (MPH), atomoxetine (ATX), guanfacine, the SSRIs fluoxetine and citalopram, and valproic acid[18]. Metformin, arbaclofen, lovastatin, trifinetide, 5-hydroxytryptamine7 (5-HT7) agonist ligands, flavonoids, and the dietary supplement sulfurophane amongst others, are still being studied[4]. More RCTs are urgently needed for individuals with ASD/ID. While studies continue to test possible treatments for the core symptoms of ASD, even experts frequently run out of options for the many comorbidities, after many medication trials including clozapine have failed. It may also turn out that no one drug will target and treat the core symptoms in ASD, given the vast heterogeneity of genetic and other causes.

Behavior analysis and psychosocial treatments play a key role in any overall management plan, since problems due to environmental factors or maladaptive learning will not respond to medication treatments. This article highlights several available older medications, with decades of community use in the general population, that show promise in ASD. Emerging evidence about them includes preliminary observed efficacy, neurotrophic effects and apparent tolerability in low dose.

ATTENTION DEFICIT HYPERACTIVITY DISORDER: EXISTING STUDIES AND EMERGING EVIDENCE ON OTHER OLD MEDICATIONS

Symptoms of attention deficit hyperactivity disorder (ADHD) include inattention, distractibility, hyperactivity and impulsivity. ADHD in ASD is often associated with dangerous behaviors including impulsive aggression and self-injury[19]. Prior to DSM-5, ADHD was not recognized as a separate diagnosis for individuals with ASD. Since it does not manifest in all individuals with ASD but does so in a large proportion, notably 28%-68%[20] it is now included as a separate diagnosis. ADHD is increasingly identified and treated in adults with ASD; a recent study found high rates of ADHD in 63 tertiary-referred adults with ASD screened for psychiatric comorbidity, notably 68% for lifetime prevalence of ADHD[9]. Additionally, ADHD is less likely to improve after adolescence in youth with ASD than in the general population with ADHD. In the community, inattentive-type ADHD is the most common subtype found in ASD/ID, however it is often untreated.

The hyperactive-impulsive subtype of ADHD has poorer outcomes in individuals with ASD, related to the more disruptive nature of hyperactivity as well as a greater likelihood of impulsive aggression, self-injury and property destruction[19]. Affect dysregulation, the inability to properly regulate and modulate emotions, was not included in DSM-5 as a diagnostic feature of ADHD, but is emphasized in DM-ID2 as an important feature in individuals with developmental disabilities including ASD. The authors of the DSM-5 ADHD criteria later published an article emphasizing affect dysregulation as an important part of ADHD[21]. ADHD-associated mood fluctuations present an important source of impairment especially in those with developmental disabilities and ADHD. Especially in adults with ASD, the ADHD diagnosis may be overlooked, resulting in a bipolar or borderline personality disorder misdiagnosis.

ADHD medications are important for improving learning, speech and language, and executive functions including inhibitory self- control. These medications improve affect dysregulation in ASD, which often manifests as impulsive aggression when the person is frustrated. Response inhibition of affective fluctuations such as laughing or crying is impaired in ADHD, related to executive function deficits. A meta-analysis of executive function in ASD found that broad executive function deficits remain stable and do not improve across development in such individuals[22]. Obsessive compulsive disorder (OCD) is very commonly associated as well in ASD, and could complicate treatment of ADHD with stimulants since the latter may increase anxiety in a dose-related manner[23]. On the other hand, non-stimulant ADHD medications may help reduce OCD and repetitive behaviors in ASD, although studies are still needed. Medications for ADHD can be divided into stimulant and non-stimulant drug categories.

When to try stimulants in ASD?

Stimulants are more likely to show efficacy and tolerability in higher-functioning individuals with ASD who have predominantly ADHD symptoms in contrast to cases with OCD symptoms, prominent repetitive behaviors or self-injury. In the latter group, non-stimulant medications may be a more tolerable choice. Young children with ASD often begin their first ADHD medication trials when their disruptive behavior interferes with education of themselves and others in the classroom. As with TD young children with ADHD, the first drug tried is usually the stimulant MPH, in divided doses three times a day, up to 1 mg/kg/day or less; individual responses vary.

Dextroamphetamine (DEX) immediate release (ir) merits study in ASD, according to the author's decades-long experience. DEX has double the potency and duration of action as MPH, notably 4 to 6 h. A meta-analysis comparing efficacy of stimulants in 23 controlled studies for ADHD found a modest advantage of amphetamines over MPH for treating ADHD in pediatric patients[24]. Divided doses given morning, lunch time, and a half-dose at 4 pm if needed, totaling approximately 0.5 mg/kg/day or less give good coverage, better than MPH. Overall, DEX ir produces less lunch-time appetite suppression, less anxiety and irritability than long-acting stimulants according to author experience.

Despite the current low level of evidence for DEX in ASD, clinical trials are warranted, and patient trials in the office may be beneficial.

However, MPH is the only stimulant studied so far in ASD, with findings of lower tolerability and lower efficacy than in TD youth. Large studies include a multisite study by the group Research Units on Pediatric Psychopharmacology (RUPP)[25], and a Cochrane database systematic review[26]. The RUPP study of 72 children with ASD, aged 5 to 13 years, found all low doses studied were superior to placebo for hyperactivity and impulsivity. Subjects were pre-selected for ability to tolerate a test dose of MPH for a week. Total doses, each given for a week, were 0.125 mg/kg, 0.25 mg/kg, and 0.5 mg/kg and were deliberately low in order to minimize side effects. However only 49% were responders, a rate much lower than the 75% response rate in TD children. Even the greatest effect size of 0.54 was significantly lower than that for ADHD response in TD children. Side effect rates were approximately double those found in TD children, and 18% exited the study early due to intolerable side effects. These included irritability, decreased appetite, and insomnia. Parent-rated lethargy, social withdrawal, and inappropriate speech increased significantly. There are also two small RCT studies and one multisite study of MPH for ADHD in ASD. Two small RCT studies of MPH for aggression in ASD found benefit over placebo on the Aberrant Behavior Checklist-Irritability (ABC-I) subscale[27-29]. Intolerable side effects were common in the latter study also, including mood changes, agitation and abnormal movements.

The Cochrane systematic review[26] of MPH in children and adolescents with ASD included 4 crossover studies, totaling 113 children ages 5 to 13 years; most (83%) were boys. There was a significant benefit on teacher-rated inattention but insufficient data to perform an impulsivity-outcome meta-analysis. Treatment duration for each dose of MPH was 1 wk. High-dose MPH significantly improved hyperactivity as rated by teachers in 4 studies, 73 subjects, ($P < 0.001$) low quality evidence, and parents in 2 studies, 71 subjects ($P = 0.02$), low quality evidence. Ratings were on the hyperactivity subscale of the ABC. MPH clinical usefulness is also limited by its short half-life of 2-4 h.

Of the long-acting stimulants in ASD, only one small study has been published. This small study of 24 children, mean age 8.8 years, found significant benefit of MPH-extended release in ASD[30]. However this was not a representative ASD sample, since the participants' mean IQ was 85.0 (SD = 16.8). MPH-ER may be useful and more tolerable for example in high-functioning individuals with ASD. Comparative studies of long-acting stimulants are lacking in ASD, including for irritability[31]. Long-acting stimulants were designed to take effect and wear off gradually, and to reduce side effects and rebound effects in the general population with ADHD. However, clinical observations suggest that in ASD, long-acting stimulants may have even greater side effects than immediate-release preparations, including worsened anxiety, appetite suppression, self-injury, lip-licking, nail-picking, trichotillomania, and compulsive behaviors, in a dose-dependent manner. The more severe the ASD, the more of a problem such side effects present, although studies are needed. Therefore, non-stimulant ADHD medications may be preferable in these individuals.

When to try non-stimulant ADHD medications in ASD?

As stated, non-stimulant ADHD medications are preferable to stimulants for individuals who have more severe ASD, and those who also have prominent OCD, RRBs and self-injury. These include ATX, alpha agonists and tricyclic antidepressants (TCAs). Clinical experience in ASD suggests that these medications can be added to low-dose stimulants that are partially helpful if the person is unable to tolerate stimulant dose increases due to side effects. Several clinical trials in TD individuals have found efficacy and tolerability of ATX in combination with stimulants, although such combinations are not FDA-approved[32]. A recent review compared responses between MPH, ATX and guanfacine in 9 controlled studies of 430 children with ASD[33]. MPH and ATX were superior to placebo for ADHD. Poorer response was found in more cognitively disabled individuals.

Atomoxetine (ATX)

ATX is a noradrenergic reuptake inhibitor shown to produce improvements in inhibitory control as part of executive functions. Importantly, acute ATX administration increased behavioral inhibition as measured by a stop-signal task in adult ADHD not accompanied by ASD[34] as well as in normal adults without either ADHD or ASD[35]. Author experience confirms that ATX may be a good choice for impulsive aggression in ASD including in adults and minimally verbal individuals, and for poor focus and disorganization in higher-functioning individuals. A randomized, multisite 10-wk double-blind placebo-controlled trial of ATX, with or without parent training, was performed for ADHD in 128 children aged 5 to 14 years with ASD. ATX showed greatest efficacy together with parent- training, but also the drug alone was superior to placebo[36]. Overall, tolerability was good, to a maximum dose of 1.8 mg/kg/day; mean dose was 1.4 mg/kg/day. Dosing was divided into twice-daily doses, to reduce side effects. The most common side effects were nausea, decreased appetite, early morning wakening and fatigue. Suicidal ideation and QTc changes were not found, in contrast to findings in children without ASD[37]. In addition, another acute RCT study of 97 youths with ASD treated with ATX, including open long-term follow-up, showed moderately improved ADHD symptoms and side effects similar to those found in studies of ATX in youth with ADHD but no ASD[38,39].

ATX trials are warranted in ADHD in adults with ASD, especially for impulsive aggression, based on author experience. The strategy is to "start low and go slow" while response is observed for, using divided doses of twice a day to improve tolerability and coverage. A recent retrospective study disputes the need for extra caution however and found similar responses to ADHD treatments in adults with ADHD and ASD to those found in a comparison group with ADHD but no ASD[40]. The therapeutic window may be narrower in minimally verbal and lower-functioning individuals with more severe degrees of ASD, according to clinical experience. Should behavioral worsening occur after an ATX dose increase, the beneficial response is usually recaptured by dose reduction.

Amitriptyline

Amitriptyline in low doses may be especially useful if used with caution, in comparison with other available non-stimulant medications, despite a lack of comparative studies. TCAs including amitriptyline are second only to stimulants in ADHD efficacy, although most evidence for their use in ADHD is from studies of the second generation TCA desipramine in youth without ASD. An advantage over stimulants according to this author's experience is that amitriptyline may benefit ADHD, anxiety, OCD, gastrointestinal pain, headaches, enuresis and insomnia[15]. Though currently there is a low level of published evidence, prospective studies are warranted, in the author's opinion. A retrospective chart review on amitriptyline[41] published by the author's group examined 50 tertiary-referred children and adolescents with ASD, ADHD and high rates of aggression and self-injury, who received low dose AMI (mean dose 1.3 ± 0.6 mg/kg/day) with mean trough blood level of 114.1 ± 50.5 ng/mL. Response occurred clinically in 60% of patients at the final visit, and in 82% of patients for at least 50% of follow-up visits. Importantly, 30% had failed ATX, and 40% had failed 3 or more other ADHD medication trials. Amtriptyline was used in combination with stimulants, most often low dose DEX ir, and also low dose risperidone or aripiprazole. In the low doses used amitriptyline did not cause complaints of constipation or urinary retention. Side effects included QTc increase on routine electrocardiogram, which did not halt treatment except in 3 cases with QTc > 440, behavioral activation and worsening of aggression. Prospective, randomized controlled studies of amitriptyline in ASD are warranted.

While a 2014 Cochrane review[42] of TCAs in TD youth showed no serious adverse events associated with taking TCAs, mild increases in pulse rates and diastolic blood pressure occurred. Of note is that the overdose risk with TCAs is lower in individuals with ASD since most individuals including adults with ASD do not self-administer their medications. TCAs should not be prescribed for use in chaotic households or those with a risk of overdose by a family member.

Alpha agonists

The class of alpha-agonist drugs is FDA-approved for ADHD in TD children but not in ASD. Since these drugs may benefit tics and Tourette disorder, they are usually a first-line treatment choice in such individuals. This drug class includes guanfacine, clonidine, long-acting guanfacine (Intuniv TM) and long-acting clonidine XR (Kapvay TM). An 8-wk multisite study of extended-release guanfacine in 62 children with ASD and ADHD, mean age 8.5 years, found a significant improvement in comparison with placebo. Modal guanfacine ER dose was 3 mg/day (range 1-4 mg/day)[43]. The most common side effects were fatigue, drowsiness and decreased appetite. For subjects on guanfacine, blood pressure dropped in the initial 4 wk, but returned almost to baseline by week 8. Pulse rate also dropped but remained lower than baseline at week 8. A small study of clonidine[44] examined response of 8 male children with autistic disorder in a double-blind, placebo-controlled crossover design for ADHD symptoms. While parent-rated Conner's questionnaire ADHD ratings improved significantly during clonidine treatment, teacher ratings were not significantly improved except for oppositional behavior. Side effects included drowsiness and decreased activity. Due to their short half-lives, the immediate-release preparations of clonidine and guanfacine should be dosed 3 times a day. Dosing is built up gradually while monitoring for dizziness, hypotension and bradycardia. Other side effects include weight gain, sedation and irritability.

Although alpha agonists improve attention, studies in otherwise TD youth with ADHD have shown their combination use with a stimulant medication produces greater attentional improvement than does either alone. Combination treatments of alpha agonists and stimulants are FDA-approved for ADHD in the non-ASD population, but not in ASD. Clinical experience suggests however that alpha agonists may be less helpful for ADHD symptoms in adults with ASD.

Thus in the author's opinion, DEX, ATX and amitriptyline may be useful additions to treatment options for ADHD comorbid with ASD, including in adults.

EXISTING ANTIPSYCHOTIC STUDIES, AND EMERGING EVIDENCE FOR OTHER ANTIPSYCHOTICS

Antipsychotics are used to treat psychosis as well as irritability in ASD, and are classified into two classes: Atypical/novel antipsychotics and typical/classical antipsychotics. ASD core symptoms

including odd, stereotyped talk on unusual restricted topics of interest are still often misdiagnosed as schizophrenia symptoms in everyday practice. Psychosis can also be confused with bizarre behavior related to subclinical seizures, in which case antiseizure medications may help. Psychotic disorders can be comorbid with ASD, including schizophrenia, delusional disorder, unspecified psychosis, or as a component of a major mood disorder such as bipolar disorder, major depressive disorder or schizoaffective disorder[45].

Typical antipsychotics

Typical antipsychotics block dopamine D2 receptors to alleviate psychosis or mania, but produce motor side effects including acute dystonias, extrapyramidal side effects (EPS), tardive dyskinesia and more rarely, neuroleptic malignant syndrome which can be fatal. Haloperidol was studied in early trials by Campbell and colleagues, in young children, but found to produce tardive withdrawal movements[46, 47] and further studies were halted. According to clinical experience, typical antipsychotics often have a lag time to onset of response in individuals with ASD, and increasing the dose early in treatment especially of high potency antipsychotics like haloperidol may result in extremely severe EPS and dysphagia after a while, especially more severely disabled individuals, with resulting joint contractures [16]. Low potency typical antipsychotics including chlorpromazine produce hypotension, slowing, cognitive dulling and weight gain in those with developmental disabilities as well as in the general population. Thioridazine produced QTc prolongation and is no longer marketed.

The medium-potency, typical antipsychotic loxapine blocks serotonin as well as dopamine, and in low doses resembles an atypical antipsychotic in positron emission tomography (PET) studies, but with less or no weight gain[48-50] which will be discussed in more detail below. Atypical antipsychotics were designed to overcome these motor side effects of typical antipsychotics by a different mechanism of action, notably by blocking serotonin as well as dopamine receptors, amongst others. However an unanticipated side effect of the atypical antipsychotics turned out to be weight gain, Type II diabetes and multiple other medical side effects[51], which are more severe in those with developmental disabilities. Atypical antipsychotics also produce possible motor side effects including neuroleptic malignant syndrome and tardive dyskinesia in the general population but also in ASD.

Atypical antipsychotics

Only two antipsychotics are FDA-approved in ASD, for children ages 6 years and older with irritability, notably risperidone and aripiprazole. The RUPP multisite 8-wk risperidone RCT study of 101 children and adolescents, mean age 8.8 years, found significant efficacy of risperidone *vs* placebo for irritability on the Clinical Global Impressions-Improvement subscale[52], and the ABC-I subscale[29] at a mean dose of 1.8 mg/day. Effect size was 1.2. Side effects included significant weight gain, appetite increase in 73%, fatigue in 59%, and drowsiness in 49%, as well as prolactin elevation. The greatest benefits reported by parents were for self-injury and aggression. Another larger multisite RCT study of risperidone and parent training in 124 children and adolescents ages 4 through 13 found that parent training could lessen the dose of risperidone needed[53]. Risperidone doses were a mean of 2.26 mg/day or 0.071 mg/ kg in the risperidone-only group, *vs* 1.98 mg/day or 0.066 mg/kg (P = 0.04, two-sided test) in the combination group of risperidone plus parent training.

Weight gain associated with risperidone treatment was marked, especially in some individuals in a double-blind crossover study performed by the author's group, of risperidone *vs* placebo for challenging behaviors in participants aged 6 to 65 with ID and ASD[54]. In a subset of 19 subjects over approximately a year, weight gain was as follows: Children (n = 5) ages 8 to 12 years gained 8.2 kg on average, adolescents (n = 6) aged 13 to 16 years gained 8.4 kg on average, and adults gained 5.4 kg on average[55]. Prolactin elevation is greater with risperidone than with other atypical antipsychotics. Breast development, galactorrhea and amenorrhea should be monitored[56]. It is important to monitor for weight gain and metabolic syndrome abnormalities, notably hypertension, glucose elevation, midline obesity, and triglyceride elevations. These are important predisposing factors for diabetes, stroke, myocardial infarction, and cognitive dysfunction and brain abnormalities[55]. In the author's experience, keeping risperidone doses low at or below 2 mg/day total, and splitting dosing to three times a day can help minimize weight gain. Importantly, clinical experience suggests that risperidone may be the most effective antipsychotic for self-injurious behavior.

A multisite RCT of aripiprazole in 218 children and adolescents with ASD, aged 6-17 years, mean age 9.3 years, found significant improvement in irritability in the aripiprazole *vs* the placebo group. Doses were 5, 10 or 15 mg/day in this 8-wk, parallel groups study. However, there was no protection against long-term relapse, the author agrees with this finding based on clinical practice, meaning that the efficacy may decrease over time, and increasing the dose may not recapture the initial good response. Side effects included sedation, the most common side effect leading to discontinuation, and significant weight gain[57]. Mean weight increases at week 8 were 0.3 kg for placebo, 1.3 kg for 5 mg/day, 1.3 kg for 10 mg/day and 1.5 kg for 15 mg/day groups, all $P < 0.05$ *vs* placebo. Importantly, aripiprazole in a low dose of 1 mg/day normalizes prolactin for example in an individual responding to risperidone who has elevated prolactin producing gynecomastia[58]. One small open pilot study compared olanzapine with haloperidol in children with autistic disorder[59] and one studied ziprasidone *vs* placebo[60] in ASD. Metformin for weight gain treatment with atypical antipsychotics was studied in a 16-wk, 4-center

multisite RCT of 60 children. Metformin was associated with reductions in future weight gain, notably body mass index (BMI) z-scores decreased significantly more from baseline to week 16 than in the placebo group (P = 0.003). However metformin did not alter lipid abnormalities, and gastrointestinal side effects identified included abdominal discomfort, abdominal pains and diarrhea[61] (in contrast to loxapine substitution discussed below).

Loxapine resembles an atypical antipsychotic at 5-10 mg/day

Loxapine shows promise clinically in adolescents and adults with ASD according to preliminary studies, and RCTs are warranted. This antipsychotic is a dibenzoxazepine tricyclic structure classified in the medium potency group of the typical antipsychotic class. Loxapine was designed in the 1980s to resemble clozapine but without the clozapine molecular component causing agranulocytosis. Loxapine has a history of extensive use in schizophrenia, usually at 40 to 80 mg/day (maximum dose of 200 mg/day) and may lack the marked weight gain and metabolic side effects of clozapine and other atypical antipsychotics[62]. A case report of a 10 year old female with autistic disorder who responded to loxapine 15 mg/day described its efficacy for treatment-resistant aggression and self-injurious behavior [63]. In low doses of 5 to 10 mg/day, loxapine resembles an atypical antipsychotic on PET brain studies, but lacks the weight gain and metabolic side effects[64,65]. A prospective 12-wk open trial of loxapine for irritability and aggression in 16 adolescents and adults with ASD[48], demonstrated that loxapine in low doses of 5 to 10 mg per day significantly improved irritability ratings on the ABC-I, with large pre- to post- treatment effect sizes on 4 subscales, d = 1.0-1.1. Fourteen of 16 subjects completed the study, all of whom had Clinical Global Impressions-Improvement scale ratings of Very Much Improved or Much Improved at week 12. Larger clinical trials are warranted.

A retrospective loxapine chart review, also by the author's group, of 15 outpatient adolescents and adults with ASD and irritability, illustrates the strategy of adding loxapine 5-10 mg/day, followed by extremely gradual taper of offending antipsychotics, which reversed weight gain, metabolic syndrome and insulin resistance including diabetes[49]. All those in the series had gained weight and manifested at least one other metabolic abnormality since starting on the baseline antipsychotic. Fourteen of the subjects were being treated with atypical antipsychotics and one received chlorpromazine, prior to addition of loxapine 5 to 10 mg daily, followed by behavioral improvement and then taper of the offending antipsychotic. Final loxapine dose in 12 subjects was 5 mg/day, and 10 mg/day in 2 subjects. At the time of chart review, all but one subject (93%) were Very Much Improved or Much Improved on CGI-I. Mean weight loss after an average of 17 mo (range 7 to 26 mo) on loxapine was -5.7 kg, with BMI reduction averaging -1.9. Mean reduction in triglycerides was -33.7 mg/dL (P = 0.03). Two subjects were tapered off metformin by their endocrinologists, and one person's insulin for Type II diabetes was discontinued. Weight loss did not differ in those already receiving metformin at the time of loxapine add-on (n = 4) though the numbers are small and the reader is therefore cautioned.

In a long-term outcomes chart review study, of 34 children, adolescents and adults with ASD, mean age 23.4 years (range 8 to 32 years), long-term low-dose loxapine at a mean dose of 8.9 mg/day (range 5 to 30 mg) was associated with lower rates of tardive dyskinesia and EPS than expected for a typical antipsychotic, mean treatment duration was 4.2 years[50]. Stahl[62] describes the addition of low doses of a classical antipsychotic to an atypical antipsychotic to "lead in" or "top up" the effect. Using loxapine add-on at 5-10 mg/day, the author has been able to minimize risperidone dose increases above 1.5-2 mg a day total of risperidone and this strategy appears weight-sparing.

Dysphagia and bowel obstruction associated with antipsychotics

A clinical word of caution is important regarding minimally verbal and neurologically impaired individuals treated with antipsychotics. Dysphagia is a common but often overlooked side effect of antipsychotics, predisposing to aspiration pneumonia and initiation of parenteral feeding after surgical insertion of gastrostomy tubes, which may then be life-long if the antipsychotic medications are not changed. Aspiration pneumonia is more common in those with severe developmental disabilities and minimally verbal individuals and those with cerebral palsy or quadriplegia treated with even moderate doses of antipsychotics, especially if the individual also receives concomitant cytochrome P450 2D6 (CYP2D6)-inhibiting SSRIs[66].

Substitution of the antipsychotic with other medications if needed, and gradual dose taper may allow swallowing improvement and normal eating reinstatement provided a repeat video swallow study is normal. A large study in non-psychiatric inpatients without ASD receiving antipsychotics mostly for delirium control found a significant association with aspiration pneumonia in comparison with a non-antipsychotic-exposed group[67]. The association magnitude was similar for typical and atypical antipsychotics. Also repeated ED and medical visits are commonly needed for ostomy revisions and infections. In clinical practice the problem is often magnified in individuals with spasticity by high dose anticholinergics such as baclofen or tizanidine. SSRIs that inhibit CYP2D6 may increase the effective dose of antispychotics and other medications such that small-appearing doses actually are effectively much larger. In addition, such prescribing practices often lead to severe constipation, paralytic ileus, bowel obstruction and resection in individuals with severe disabilities. The author avoids using loxapine in individuals with severe disabilities and uses low dose risperidone in divided doses instead, due to the elevated dysphagia and EPS risks.

SSRI STUDIES IN ASD; AND WHAT DRUGS MAY HELP RRBs?

SSRI studies have not demonstrated efficacy for RRBs

While SSRIs may initially appear to help anxiety, depression and compulsive behaviors they may later worsen problems significantly and produce behavioral activation, especially in higher doses, in a dose-related manner. A 12-wk RCT study of 149 youth aged 5 to 17 years with ASD treated with citalopram, dosed up to 20 mg daily (mean dose 16 mg/day) for RRBs in ASD, was negative[68]. Overall there was no change in repetitive behavior but also significant side effects occurred. These included impulsiveness, increased energy level, hyperactivity, decreased concentration, increased RRBs, insomnia, diarrhea and skin dryness and itching.

A 14-wk RCT study of 158 youth aged 5 to 17 years with ASD, treated with fluoxetine found no differences from placebo for RRBs as rated on the Child Yale-Brown Obsessive Compulsive Scale-Pervasive Developmental Disorders version[69]. Another fluoxetine RCT was also negative; Australian investigators randomized 146 youth aged 7.5 to 18 years with ASD to fluoxetine (20 mg/day if < 40 kg or 30 mg/day if ≥ 40 kg) or placebo. Any differences favoring fluoxetine were statistically nonsignificant after variables of gender, verbal abilities and baseline differences were controlled for. There was also no significant trend toward improvement on secondary outcome measures of RRBs, irritability, anxiety or global change[70]. An older, smaller RCT study of 39 youths aged 5-16 years found that a mean dose of 9.9 mg/day of fluoxetine was superior to placebo[71], however this has not been replicated. Some individual case studies and a case series suggested fluoxetine response however[72].

SSRIs are the most commonly prescribed drugs in ASD[4], although their use is not backed by study evidence. In the author's experience they may be helpful in high-functioning individuals with ASD for anxiety or depression. The Cochrane collaboration literature review of SSRIs in autism found no overall benefit in ASD, weighing positive and negative studies against each other[73]. In the author's experience, non-stimulant ADHD medications rather than SSRIs can help OCD and repetitive behaviors, including ATX and amitriptyline, this is anecdotal evidence but could be worth a try in the clinic. Many times the patient is presenting on an antipsychotic already. RRBs may relate also to ADHD symptoms, notably impulsivity, as part of a common cognitive impairment of executive function ("putting the breaks on") *i.e.* non-specific response inhibition[74]. These investigators found significant associations between repetitive speech and impulsive speech, between stereotyped behavior and overactivity, and between restricted preferences and impulsivity. This study further justifies the argument for studying non-stimulant ADHD medications for RRBs.

The TCA clomipramine reduced RRBs in one small study

Two TCAs typically targeting OCD, repetitive behaviors and hyperactivity, notably clomipramine and desipramine were compared with placebo in one double-blind study[75]. The investigators compared clomipramine to placebo in 12 subjects with autism using a crossover design, together with 12 different subjects completing a parallel trial of clomipramine *vs* desipramine. Clomipramine was superior to placebo and desipramine in reducing ratings on stereotypies, compulsive ritualized behaviors ($P < 0.05$) and anger, while desipramine was no different from placebo except in reducing hyperactivity. However in the author's experience substitution of amitriptyline for clomipramine in patients who present on clomipramine has produced greater global clinical improvements. This was an empirical observation made by the author's team in the 1990s that appears valid still today[41].

In a small cross-over study, 5 of 18 children (28%) treated with low dose fluvoxamine responded[76]. Fluvoxamine was found to benefit RRBs, maladaptive behavior, aggression and language in a small 12-wk RCT of 30 adults with autistic disorder[77]. Treatment studies of SSRIs or other classes of agents for depression and for suicidal behavior in ASD are lacking. For anxiety disorders in general in ASD, some smaller studies suggest the efficacy of citalopram, and some were positive for buspirone. One buspirone study in ASD found worsening of aggression and self-injury[78].

Maintenance benzodiazepines are avoided as a general principle in individuals with developmental disabilities, except for insomnia and as pre-sedation for blood tests and other procedures including dental work. Downsides include disinhibition effects, cognitive slowing and impairment, clumsiness, falls and injuries associated with benzodiazepine treatment.

HOW TO APPROACH ANTI-SEIZURE MEDICATIONS?

The therapeutic behavioral effects of anti-seizure medications in ASD for use other than seizures are inconclusive, according to available evidence. An RCT by the author's team of valproic acid for aggressive behavior in youth with ASD was negative, although some subjects appeared to benefit from it, likely related to the heterogeneity within ASD[79]. Another study found valproic acid to be beneficial for RRBs in ASD, however this finding has not been replicated. Worsening of behavior occurred in 4 of 13 cases[80]. Divalproex was effective for controlling irritability associated with fluoxetine treatment in ASD[81].

Clinical experience suggests a trial of anti-seizure medication such as valproic acid or lamotrigine (LTG) may be beneficial especially if seizures are known or suspected, and the presentation of behavior problems is bizarre or atypical. This pertains especially to minimally verbal individuals with severe ASD, who have very high rates of seizures, and those with a known history of traumatic brain injury.

For mood disorders

Apart from ADHD, bipolar disorder is another, much less common cause of impulsive aggression in ASD. A 25% lifetime prevalence for bipolar disorder *vs* 68% for ADHD was found in a tertiary-referred population of high-functioning adults with ASD[9]. Minimally verbal individuals may also present with bipolar-like illness however studies of this portion of the ASD spectrum are still needed. Although lithium may be helpful, anti-seizure medications are a first line of treatment for bipolar disorder in individuals with developmental disabilities.

Divalproex and carbamazepine

Mood-stabilizing anti-seizure medications including divalproex and carbamazepine are the first-line treatments for mania, mixed or rapid cycling bipolar disorder in the general population[82] as well as in individuals with developmental disabilities. Valproate/divalproex is FDA-approved for bipolar mania but not for acute bipolar depression in the general population. Divalproex can also be effective for acute mixed bipolar disorder[83]. Side effects include weight gain, polycystic ovarian syndrome, low blood platelets, alopecia, elevated liver enzymes and less often pancreatitis. In addition, divalproex can cause ASD if taken in early pregnancy[84]. Weight gain, hepatic enzymes and blood cell counts require monitoring.

Both divalproex and carbamazepine are available in extended-release formulations. Carbamazepine is weight-neutral but side effects may include nausea, vomiting, dizziness, drowsiness, dry mouth, constipation and unsteadiness. A rare but extremely serious potential side effect of carbamazepine is Stevens-Johnson syndrome, which may start as an influenza-like illness but progress to a blistering skin rash, skin peeling and death.

Lamotrigine (LTG)

LTG is the mood-stabilizing anti-seizure medication of choice for bipolar depression treatment as well as prophylaxis[85]. Apart from the vigilance needed for a serious skin rash again associated with Stevens-Johnson syndrome, and the need to start LTG slowly to try and prevent this, the longer-term profile of LTG is favorable in comparison with other anti-seizure medications. Another important use for consideration in psychiatry, according to author experience, is for suspected seizures including spells of eye-blinking, mouth movements or disorientation episodes accompanied by bizarre behavior presentations in ASD, as mentioned above.

Evidence for LTG is weaker for acute bipolar depression and rapid cycling bipolar disorder in the general population. LTG must be started extremely slowly by adding a low dose every 1 to 2 wk, and even more gradually if the individual is receiving divalproex (adding 25 mg every 2 wk), to avoid a potentially life-threatening skin rash that begins on the upper chest region. Skin rash signs include skin peeling, blistering, hives, itching and painful sores in the mouth or around the eyes. Other LTG side effects include blurred or double vision, poor motor coordination, headache, drowsiness, and difficulty thinking or speaking.

Gabapentin

Gabapentin is an add-on anti-seizure medication often prescribed off-label in psychiatry for various indications despite negative RCTs including for bipolar disorder. Rather than acting on gamma-amino butyric acid, gabapentin likely acts on calcium channels in the brain and spinal cord, and has few drug interactions since it is renally excreted. Gabapentin add-on to valproic acid and low dose antipsychotic was helpful in an open study by the author, in adults with developmental disabilities[86]. Gabapentin in divided doses 3 times a day, totaling 900 to 1800 mg a day were effective as add-on to valproic acid and low dose antipsychotic, and also in a subset replaced lithium and thus eliminated lithium side effects. Gabapentin side effects included dizziness and clumsiness; to prevent these it was started at 100 mg daily and increased slowly by only 100-200 mg per week, although prospective RCT studies are needed.

While lithium is still used in ASD, the side effects are often worse in those with developmental disabilities, and include polydipsia and polyuria (excessive thirst, drinking and enuresis) and tremor. Acute toxicity is a medical emergency requiring dialysis and intensive care units treatment, and is a greater risk in individuals with disabilities. Vomiting, diarrhea, failure to drink fluids for any reason, and certain medications including the angiotensin-converting enzyme inhibitor losartan predispose to toxicity[86].

Insomnia is very common in ASD and should not be interpreted as mania-related illness unless accompanied by other observable mania features. Another pitfall is that loud, rapid speech and outgoing personality may not be due to bipolar disorder but an enduring personality trait with a life-long history.

Anti-seizure medication-related behavioral side effects

Importantly, several anti-seizure medications while benefitting seizures may produce adverse behavioral effects. The latter may not have been considered by the neurologist if the seizures are adequately controlled. Therefore identification of such side effects by the psychiatrist is essential. Barbiturate-based anti-seizure medications including phenobarbital and phenytoin, and benzodiazepine-based medications, as well as vigabitrin often worsen behavior. Such medications may lead to an ADHD-like picture of affect dysregulation, hyperactivity, restlessness, impulsive aggression and self-injury[87]. Carbamazepine, oxcarbazepine, levetiracetam and topiramate may also worsen hyperactivity, mood or psychotic symptoms or other behavior problems. LTG and divalproex may be less likely to have behavioral side effects in adults with ASD according to clinical experience.

IN SUMMARY

Studies included followed a broad and thorough literature review of pharmacotherapy in ASD, in order to provide a clear overview of the topic as well as the author's expert opinion. For a summary of key points for pharmacotherapy in ASD (Table 1). Limitations of this opinion review include that aside from evidence-based guidelines, prescribing practices may be extremely variable, not only by country and region, but also by individual practitioners who may find other medications useful in ASD. The author has however attempted to provide a personal but balanced view overall. Regarding future drug treatments for core ASD symptoms it may not be possible for one drug to target and treat all of the many subtypes of ASD, given the many genetic and other causes. Of note is that while certain drugs such as ATX may not be available in all countries, amitriptyline is approved in many countries and is available in generic forms.

CLINICAL PEARLS GLEANED OVER MANY DECADES OF RESEARCH AND PRACTICE TREATING ALL AGES WITH DEVELOPMENTAL DISABILITIES

Environmental and emotional causes are more likely to respond to behavioral consultation: This can be key also in treatment resistance

It is important to emphasize that environmental and emotional causes of behavior problems will be more likely to respond to behavioral consultation and psychosocial interventions. Of late, there has been greater recognition of environmental contributors to psychiatric illness in the field in general. Abuse of all types is also more likely in vulnerable individuals such as those with developmental disabilities. Taking a detailed longitudinal history is essential, regarding likely environmental stressors such as family deaths or job losses, moves and staff changes leading to frustration and severe "protest" behavior problems including aggression, before making psychiatric diagnoses and trying medication treatments. Protest behaviors and use of aggression as communication are more likely especially if the individual has demonstrated consistently good functioning over one or more periods of time in their past. A developmental and childhood psychiatric history is also essential to understanding of presenting problems. Irritability can result from many non-psychiatric causes, including medical illness, lack of sleep, general frustration or unhappiness with a living situation. Treating just dimensional behavior problems, such as irritability or hyperactivity with single medications may be feasible for milder cases. As in other branches of medicine, if the diagnosis is wrong then the treatment will unlikely help.

Closer examination for ADHD and trying ADHD treatments pays off, including in females and adults with severe disabilities

This applies to ADHD wrongly diagnosed as bipolar disorder, since antipsychotics and mood stabilizers do not adequately treat ADHD-related impulsivity. This was a personal lesson the author learned early on in practice after specializing in treating this population. Females diagnosed with depression and recurrent suicidality may also respond to ADHD treatments, allowing for cautious taper off of antidepressants. Parents and caregivers often describe a person with ADHD person as "anxious" since they rarely sit still, and "moody" due to lack of affect regulation associated with easy crying or laughing spells.

DEX, ATX and amitriptyline are useful for ADHD comorbid with ASD

Impulsive aggression such as cussing, hitting, kicking, biting, pinching and running off may respond to one or more ADHD treatments if the ADHD history and diagnosis are elicited. Many adults already received treatment for ADHD as children but once transitioning services happens the ADHD diagnosis is overlooked. Although only studies in TD individuals are available as discussed above, a combination of low dose stimulant together with a non-stimulant ADHD medication such as ATX, amitriptyline or guanfacine may be needed. Low dose risperidone may also be used in combination with the ADHD

Table 1 Key points for pharmacotherapy in autism spectrum disorders

ADHD medications	Antipsychotic medications	Anti-seizure medications
Stimulants for high-functioning ASD: (1) Methylphenidate in young children; and (2) Dextroamphetamine immediate release in children, adolescents and adults is often useful	Risperidone: Especially useful for self-injurious behavior: Also useful in children for irritability and aggression in low, divided doses	Phenytoin and phenobarbital frequently worsen behavior. Replace with newer medications in consultation with neurologist
Non-stimulants for lower-functioning ASD: (1) Atomoxetine; (2) Amitriptyline; and (3) Guanfacine in low, divided doses if tics/Tourette disorder	Loxapine at 5-10 mg/day: Useful in adolescents and adults for irritability, aggression, or with risperidone as a weight-sparing strategy	Levotiracetam, carbamazepine, benzodiazepines, and others may also adversely affect behavior
For greater effect: Low-dose combination of stimulant and non-stimulant medications may be tried	Watch out for the following, especially with high-dose antipsychotics: Difficulty in swallowing or bowel obstructions in more severely disabled individuals	Gabapentin may be useful as an add-on to divalproex for bipolar disorder, instead of lithium

Selective serotonin reuptake inhibitors may reduce anxiety or depression in high-functioning individuals but are unlikely to alleviate repetitive/compulsive behaviors in autism spectrum disorders, and often cause activation and behavioral worsening. ASD: Autism spectrum disorders; ADHD: Attention deficit hyperactivity disorder.

treatments, although again only one study in the TD participants is available regarding this[88].

Two ADHD medications may be needed (stimulant and non-stimulant) possibly also together with low dose antipsychotic such as risperidone in moderate-to -severe cases with aggression. In the author's experience, ATX is frequently clinically useful for ADHD with impulsive aggression, including in more severely disabled individuals. The tolerable doses may be lower than in higher functioning individuals, although improvements may be regained if the dose is decreased again after behavioral worsening following a dose increase occurs. More studies are warranted. Amitriptyline in low doses can be extremely helpful for cases with insomnia, headaches, gastrointestinal issues, ADHD, impulsive aggression and OCD, used with caution and watching for drug interactions. Studies are warranted of amitriptyline for RRBs in ASD according to author experience.

Are RRBs part of the ADHD spectrum, and could they respond to ADHD treatments?

The study by Burbridge and coworkers[74] leading to the concept of RRBs as related to ADHD, in other words a type of motor impulsivity, may be key to guiding future studies for RRB etiology and treatments. One study found ATX was somewhat effective for RRBs in youth with ASD, which is promising[39]. No known treatment currently exists for core ASD features, likely due to the heterogeneity and many different genetic causes. Metformin, arbaclofen, lovastatin, trifinetide, 5-HT7 agonist ligands, flavonoids, cannabidiol, cannabis and the dietary supplement sulfurophane amongst others, are still being studied[4].

Risperidone remains useful in youth with severe irritability and may be helpful for self-injury; dose at ≤ 2 mg/day in divided doses

Dosing risperidone at or below 2 mg/day given in divided doses may mitigate weight gain and metabolic side effects, though individuals vary in this regard. Another author observation is that risperidone may be the most effective medication for self-injurious behaviors including self-biting, head- banging, self-hitting and others. Weight gain and metabolic side effects require monitoring.

Loxapine at 5-10 mg/day resembles an atypical antipsychotic but likely with emerging safety evidence of a more favorable metabolic profile

Loxapine is one of the main antipsychotics now used in practice by the author and several colleagues in other regions, for adolescents and adults with ASD, related to an empirical finding made over 2 decades ago and then the preliminary published studies discussed above. Addition of 5-10 mg/day of loxapine often produces significant clinical improvement in irritability and aggression, which if needed then allows very gradual taper of other antipsychotics which have caused excessive weight gain or produced too little response. While a common practice may be to follow schizophrenia guidelines and convert a treatment-resistant person to a depo antipsychotic, hoping for improved aggression control, adding loxapine, in the author's experience produces superior results overall. However loxapine is likely not suitable for more severely disabled individuals due to its potent dopamine blocking action that may cause dysphagia in them; low dose risperidone may be preferable in this setting. Olanzapine is another cause of dysphagia in those with more severe disabilities, according to clinical experience.

Gabapentin may be a useful add-on to divalproex and low dose antipsychotic if lithium is not a good choice for the individual patient

Published preliminary evidence on gabapentin add-on to valproate and low dose antipsychotic in ASD

may be useful when lithium is not tolerated due to side effects, or if lithium toxicity has already occurred once or more. Studies are needed.

SSRIs may be helpful in higher-functioning ASD for anxiety or depression, but not for RRBs

SSRIs remain the most widely prescribed drug class in ASD in the United States overall. Recent negative studies of citalopram and fluoxetine for RRBs in youth with ASD are helpful in this clarification. In many cases, high dose SSRIs worsen OCD and agitation, while gradual SSRI taper may lead to clinical improvements. Also, in cases involving SSRIs increasing the effective antipsychotic dose due to CYP2D6 inhibition, swallowing impairment and bowel motility problems may be reversed by gradual SSRI taper and medication revisions.

CONCLUSION

Existing studies in ASD are useful guides for clinical practice, but many more are still needed. Most prescribing in individuals with developmental disabilities is of clinical necessity off-label. Some older psychotropic medications with emerging evidence may extend and improve possible successful treatment options for clinicians serving individuals of all ages with ASD and severe behavior problems. Until controlled studies of these drugs become available, cautious clinical use starting with low doses and minding drug interactions may be justified. Another important focus should be alerts regarding possible ADHD with impulsive aggression, especially in females and in adults with ASD. The older medications worth trying include, but are clearly not limited to, DEX, ATX and amitriptyline for individuals with ADHD associated with impulsive aggression.

For irritability and psychotic comorbidity in adolescents and adults with ASD, preliminary published evidence and clinical experience point to loxapine in doses of 5-10 mg/day having atypical antipsychotic properties but likely with lower metabolic risk associated. For likely seizure activity associated with bizarre behaviors that is unable to be worked up *via* electroencephalogram due to lack of cooperation, LTG may be considered, especially in those with severe disabilities since they have higher rates of seizures. No medications have been identified and replicated so far to treat the core symptoms of autism, including RRBs. Drugs without demonstrated benefit for core symptoms include risperidone, oxytocin, bumetanide, buspirone, citalopram, fluoxetine, fluvoxamine and N-acetyl cysteine. While SSRIs are the most commonly prescribed drugs in ASD and may help individual patients, recent RCT studies did not show significant efficacy for RRBs in ASD, but rather a significant side effect burden including behavioral activation. Clinical trials of the older drugs discussed are warranted. All medications should be used in conjunction with other multimodal therapies including behavioral consultation, and selected for the individual patient.

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REVIEW

Operational definitions and measurement of externalizing behavior problems: An integrative review including research models and clinical diagnostic systems

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Abstract

Measurement of externalizing disorders such as antisocial disorders, attention-deficit/hyperactivity disorder or borderline disorder have relevant implications for the daily lives of people with these disorders. While the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) have provided the diagnostic framework for decades, recent dimensional frameworks question the categorical approach of psychopathology, inherent in traditional nosotaxies. Tests and instruments develop under the DSM or ICD framework preferentially adopt this categorical approach, providing diagnostic labels. In contrast, dimensional measurement instruments provide an individualized profile for the domains that comprise the externalizing spectrum, but are less widely used in practice. Current paper aims to review the operational definitions of externalizing disorders defined under these different frameworks, revise the different measurement alternatives existing, and provide an integrative operational definition. First, an analysis of the operational definition of externalizing disorders among the DSM/ICD diagnostic systems and the recent Hierarchical Taxonomy of Psychopathology (HiTOP) model is carried out. Then, in order to analyze the coverage of operational definitions found, a description of measurement instruments among each conceptualization is provided. Three phases in the development of the ICD and DSM diagnosis systems can be observed with direct implications for measurement. ICD and DSM versions have progressively introduced systematicity, providing more detailed descriptions of diagnostic criteria and categories that ease the measurement instrument

development. However, it is questioned whether the DSM/ICD systems adequately modelize externalizing disorders, and therefore their measurement. More recent theoretical approaches, such as the HiTOP model seek to overcome some of the criticism raised towards the classification systems. Nevertheless, several issues concerning this model raise mesasurement challenges. A revision of the instruments underneath each approach shows incomplete coverage of externalizing disorders among the existing instruments. Efforts to bring nosotaxies together with other theoretical models of psychopathology and personality are still needed. The integrative operational definition of externalizing disorders provided may help to gather clinical practice and research.

Key Words: Externalizing disorders; Measurement; Diagnostic and Statistical Manual of Mental Disorders; International Classification of Diseases; Hierarchical Taxonomy of Psychopathology; Psychopathology

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Core Tip: Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases have evolved as a clinical tool but with several limitations associated to the operational definition for measuring externalizing disorders. Approaches such a Hierarchical Taxonomy of Psychopathology improve the conceptualization giving a general framework for psychopathology, although providing a more complex solution for clinicians. Present review shows a lack of measurement instruments integrating new theoretical advances and clinical utility.

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INTRODUCTION

The measurement of mental disorders, like any other construct, is a complex process. In addition, unlike other psychological constructs, the measurement of mental disorders can have important implications for the daily lives of people with these disorders and their relatives. Mental disorders in the externalizing spectrum [*e.g.*, antisocial disorders, attention-deficit/hyperactivity disorder (ADHD), borderline disorder] are characterized by problematic behaviors that involve the self and especially interpersonal functioning[1,2]. Thus, these disorders can impact the educational development of young people[3,4] work activity[5], and even cause problems with serious legal consequences[6,7]. Thus, the correct diagnosis of these disorders will not only allow for adequate therapeutic planning but may also affect the living conditions of those affected. In this regard, and as established by the Standards for Educational and Psychological Measurement[8], the development of appropriate measurement instruments for these disorders requires a careful process of design, application, and interpretation of their scores.

Various tests have been developed for measuring externalizing disorders and associated problem behaviors based on various operational definitions. In this respect, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) have been the main theoretical bases for the development of a wide variety of these measurement instruments[9,10]. However, these nosotaxies have been updated in successive editions of these manuals, leading to changes in the diagnostic criteria used to operationalize externalizing disorders. In addition, another set of tests widely used as diagnostic tools was developed outside these classifications[11,12]. One example is the Wender-Utah Scale (WURS), which uses the operational definition of ADHD based on the Wender-Utah criteria[13,14].

In parallel to the above, new theoretical approaches have emerged in recent years that address the conceptualization and classification of these disorders from a dimensional approach. Some of these models focus on personality disorders (PDs), including externalizing disorders, such as the Alternative Model of PDs (AMPD)[15] and the ICD-11 personality model[16]. Other models include PDs and other psychopathological disorders within the externalizing spectrum. These include the Hierarchical Taxonomy of Psychopathology (HiTOP) model[17] or the conceptualization of externalizing behaviors proposed in the Minnesota Multiphasic Personality Inventory (MMPI)[18]. The variety of theoretical approaches to externalizing disorders implies a multitude of operational definitions for these disorders.

Therefore, the tests used to measure them use different content. That is, each operational definition generates a test that is conceptually different from the rest, and it is necessary to reflect on the extent to which tests with different operational definitions are measuring the same mental disorders, thus allowing for a comparison of their results and applicability.

In the field of measurement, it is necessary to differentiate tests that measure externalizing disorders to obtain a diagnostic label from those aimed at obtaining a dimensional psychopathological profile. The former is most commonly theoretically based on the DSM or ICD and preferentially adopts a categorical approach. That is, they use scoring systems that allow differentiation between the presence or absence of a disorder [*e.g.*, Structured Clinical Interview for DSM (SCID)[19-21], Composite International Diagnostic Interview (CIDI)[22]] or in three or four categories according to the severity of the disorder [23,24]. Due to the parsimony and utility of categorical measures, these have been the most widely used in both research and clinical settings, being considered particularly suitable for decision-making in a multitude of contexts (*e.g.*, social, judicial, and clinical). In addition, for such instruments, it is desirable to estimate their reliability through test-retest procedures and to provide evidence of validity based on expert judgment, as well as on the sensitivity and specificity of the scores.

In contrast, dimensional measurement instruments provide an individualized profile for the domains that comprise the externalizing spectrum. Examples of these tests are the Adult Self Report (ASR)[25]; the MMPI-2[18] and the Personality Assessment Inventory (PAI)[26,27]. These profiles are determined by applying a set of items that assess facets, traits, or behaviors on dimensional scales and whose combination of scores provides the possible presence of one or other disorders. This scoring system has become more relevant in recent years due to the possibility of carrying out transdiagnostic interventions [28]. However, these dimensional instruments are less widely used in practice. This is due, on the one hand, to the difficulties in generating a diagnostic label from these instruments, while on the other hand, fewer instruments are available within these approaches, with the majority only used for assessing personality traits.

Given the issues associated with the operational definition and scoring systems of the tests, a review of the specialized literature advocates the benefit of using dimensional models, as they more adequately capture the nature of the disorders[29-31]. However, it should not be forgotten that, to date, clinical practice is strongly associated with using categorical diagnoses. In this sense, some authors propose the need to adopt a hybrid conception, according to which it is possible to use tests with dimensional scores but indicating cutoffs that allow for identifying the presence or absence of a disorder[32-34]. While this approach can be practical and useful, when applying such instruments we should not overlook the impact on measuring the disorder in terms of content validity. With this in mind, this paper aims to review the theoretical frameworks underpinning the operational definitions used in the design of tests that assess externalizing disorders along with the most frequently used tests and their various implications. Finally, a proposed operational definition for a test is presented that integrates different theoretical perspectives, with the aim of achieving conceptual equivalence.

OPERATIONAL DEFINITIONS FOR MEASURING EXTERNALIZING BEHAVIORS

The specialized literature review reveals the existence of multiple and diverse theoretical frameworks that have helped to develop tests to measure externalizing disorders or problem behaviors. The analysis of operational definitions allows us to differentiate between those that use the criteria specified in the DSM and ICD diagnostic classification systems and another set of tests that use operational definitions based on other psychopathological models. In addition, the analysis of these definitions allows a better contextualization of the utility and relevance of each measurement instrument. The main theoretical frameworks used, and their operational definitions are discussed below.

Operational definitions based on the DSM/ICD classification systems

The DSM/ICD classification systems have generated versions with varying degrees of modification in their diagnostic criteria. From the first versions of these nosotaxies in the 1950s to the current DSM-5 and ICD-11, it is possible to identify three main stages concerning the definition of mental disorders, which have affected the operational definitions of the tests developed: (1) A first stage in which disorders were conceptualized through brief clinical or phenomenological descriptions (DSM-I and DSM-II, and ICD-6 to ICD-9); (2) A second stage that involved a paradigm shift, such that disorders are operationalized through the presence of a given number of diagnostic criteria (DSM-III to DSM-IV-TR, and ICD-10); and (3) Finally, a third stage characterized by the incorporation of diagnostic criteria and traits to be assessed in dimensional terms, particularly in PDs.

In the first stage, an analysis of the first versions of the ICD-6[10] and DSM-I[9] nosotaxies has revealed that the categories included in these diagnostic systems did not include operational definitions *per se*. ICD-6 aimed to serve as a statistical classification system rather than a diagnostic system, incorporating only the different categories and associated numerical codes, while the DSM-I provided brief clinical descriptions characterizing each disorder. The assessment and measurement of the disorders were based on the judgment of the clinician or researcher who relied on the descriptions

provided by DSM-I. Concerning the disorders, ICD-6 included 26 diagnostic categories, grouped into three major groups: Psychosis, psychoneurotic disorders, and disorders of character, behavior, and intelligence. These categories were maintained in the ICD-7 version[35], except for corrected errors. The descriptions provided in the DSM-I were based on psychodynamic etiologies resulting from the prevailing American trend at that time. In this sense, the DSM-I defined disorders as "reactions", emphasizing that the subject's maladaptation to environmental stressors could be the cause of the mental disorder.

The ICD-8[36] and DSM-II[37] versions introduced changes to increase their systematicity. Specifically, ICD-8 provided a glossary of descriptions of the diagnostic categories, and, as in DSM-II and ICD-9[38], the descriptions are incorporated directly into the diagnostic categories. Including these descriptions favored the development of instruments for measuring disorders, providing the first operational definitions. In addition, it should be noted that among the two nosotaxies, some categories were unified, which led to a convergence in the measurement of disorders using both classification systems.

In summary, this first stage comprises the versions ICD-6 (1948), DSM-I (1952), ICD-7 (1955), ICD-8 (1967), DSM-II (1968), ICD-9 (1975), characterized by the absence of a definition based on operational criteria. However, each new version shows a tendency toward greater categorization and specificity. This was evidenced by an increased specificity of the recognized mental disorders collected in multiple subdivisions of the disorder categories (*e.g.*, eight new alcoholic brain syndromes were defined). Moreover, the definition of mental illness was broadened to include not only the more severe extremes of psychopathology but also milder symptoms that might be observed in the general population and not exclusively in the clinical population.

The fact that measurement was left completely open to interpretation by the clinician limited the use of early versions of the nosotaxies for systematically measuring mental disorders. Criticism soon emerged against the absence of criteria, the use of diagnostic labels without an identity of concepts, and poor reliability of clinical judgment due to interpretative ambiguity arising from the narrow definitions [39-41]. It is not surprising, therefore, that measurement instruments for mental disorders in this early stage were scarce in the literature. A bibliographic search in the Pubmed and PsycInfo databases with the keyword "assessment", confined to the years corresponding to these editions of the classification systems (between 1948, year of publication of ICD-6, and 1980, year of publication of DSM-III), reveals, firstly, the non-existence of diagnostic instruments based on the first versions of the DSM and the ICD. The existing instruments at this stage (*e.g.*, Assessment of Personality[42]) offer measures framed within psychopathological models far removed from these nosotaxies. In the words of Mayes and Horwitz[43], large-scale clinical research based on these versions of diagnostic systems was impossible since the lack of reliable diagnostic categories in the manuals prevented replication by researchers.

The beginning of the second stage of establishing definitions of disorders from nosotaxies was marked by the publication of DSM-III[19]. This version constituted a shift in the psychiatric paradigm of classification systems[44] and thus in the definition of disorders. Advances in psychometrics were applied to psychiatric assessment, leading to a tendency towards quantifying disorders through tests, rating scales, and checklists, which became a standard in mental health research and practice. In turn, the declining use of psychodynamic paradigms led to the abandonment of psychodynamic terms and etiologies, which were difficult to measure psychometrically[45-47].

To a large extent, the operational definitions proposed in this second stage aimed to achieve reliable and valid diagnoses from a metric perspective. To this end, expert consensus was used to define the diagnostic criteria[48], which were used to operationally define the tests. However, it should be noted that the delimitation of diagnostic criteria followed a descriptive approach as opposed to biological or psychological models. Therefore, this conceptualization has been described as atheoretical, its aim being to describe signs or symptoms without proposing explanations or etiological models[45,49]. Furthermore, it is worth noting the polythetic nature of the criteria included in the diagnostic systems of this second stage. That is, the operational definition encompassed criteria in which no particular one was necessary but instead required a combination of various criteria from a defined set. Consequently, the measurement of disorders derived from this scoring system made it possible for two people to obtain the same diagnosis despite being phenotypically different based on their diagnostic criteria.

Another noteworthy aspect from a psychometric perspective is that, at this stage, the diagnostic criteria refer to a level of impairment or dysfunction of individuals. That is, thresholds are implicitly set for deciding whether the presence of a symptom generates significant distress and impairment for individuals and their context[50]. However, an individual assessment of each clinician and researcher was used to determine the level of impairment, and therefore it was open to interpretation and subject to ambiguity depending on who made the diagnosis. In any case, the inclusion of this assessment showed the need to differentiate between normal and pathological[51]. Consequently, on the one hand, measures of functioning began to emerge that sought to operationalize and measure the term dysfunctionality to support a clinical judgment of the level of impairment (*i.e.*, Health-Sickness Rating Scale, Global Assessment Scale). On the other hand, these scales - which initially appeared independently of the classification systems - were subsequently adopted by them. Thus, from DSM-III-R[52] onwards, the Global Assessment of Functioning Scale[53,54] and the Global Activity Evaluation Scale were incorporated as a measure of functioning in axis V of DSM-IV[55]. In the case of the ICD, dysfunc-

tionality was measured through the incorporation of the World Health Organization Short Disability Assessment Schedule[56], included in axis II of the Multiaxial Adult Version of the ICD-10 version[57]. On the other hand, symptoms were identified that caused clinically significant distress to individuals. However, they did not have a syndromic entity *per se,* leading to the emergence of the category "not otherwise specified".

Finally, from a psychometric standpoint, it was also important to organize externalizing disorders into different sections. Thus, impulse control and substance use disorders were included in one group (Axis I), while PDs (narcissistic, histrionic, paranoid, borderline, and antisocial) were included in Axis II [52,58]. This separation of disorders has repercussions for the operational definition of the disorders, considering PDs as a different entity from other psychopathological disorders, thus using different terms to definition one or the other section. Axis I disorders were mainly defined based on symptoms or signs. In contrast, Axis II disorders were defined on the basis of traits, the latter being considered more stable psychopathological attributes. As a result of this approach, tests based on nosotaxies are also distinguished according to whether the items assess symptoms (psychopathology) or traits (personality).

While this conceptualization of externalizing disorders and behaviors has had many positive consequences for their measurement, it also has limitations in psychometric terms. The World Health Organization pointed out that the definitions proposed in the ICD-10 version did not provide sufficient information for a reliable implementation of the diagnoses in the clinical context[59]. Therefore, to improve diagnostic reliability, several guidelines were published providing definitions and instructions for establishing diagnoses (Clinical Descriptions and diagnostic guidelines[59] and Diagnostic Criteria for Research[60]). In addition, diagnostic interviews incorporated as items transcriptions of the diagnostic criteria for nosotaxies, including indications on the inclusion or exclusion of diagnoses.

Finally, it should be noted that despite attempts during this stage to unify criteria between the different nosotaxias emerging from the World Health Organization and American Psychological Association, some authors argue that only a very small proportion of these categories are similar[61]. Consequently, diagnostic tools derived from these classification systems may provide a clinical diagnosis with a similar label, albeit based on different operational definitions.

The third stage in the operational definitions of nosotaxias is found in the recent DSM-5[15] and ICD-11[16] versions. Here, the changes in the conceptualization of the disorders mark the beginning of a paradigm shift in the operational definitions of the disorders. On the one hand, both versions aim to improve the clinical utility of the diagnostic criteria and to ground existing etiological and neurobiological research in the definitions of disorders, thus providing a theoretical framework for their classification. Similarly, one of the main changes was to introduce emerging evidence in favor of dimensional models into the conceptualization of psychopathology. In this sense, changes have been made concerning substance use disorder that affect its operational definition, unifying the concepts of abuse and dependence. In addition, some diagnostic criteria have been eliminated, while new criteria have been incorporated. There has been a shift from a categorical to a dimensional diagnosis, where the addition of diagnostic criteria has repercussions for diagnosing the severity of dependence. Likewise, changes affecting the operational definition of ADHD have also been noted, primarily the need to present fewer symptoms to diagnose ADHD in adults.

However, the main changes observed in both nosotaxias are associated with PDs. Although the DSM-5 proposes a diagnostic approach that maintains the DSM-IV criteria to preserve continuity with clinical practice, it also includes in a final section (section III) an AMPD that defines two criteria for the identification of PD. Criterion A establishes the need to assess personality dysfunction, while criterion B assesses 25 facets and traits organized into five more general personality domains, providing the typology of that dysfunction. The assessment of the 25 facets allows delineating a dimensional psychopathological profile, and the identification of elevation in certain facets indicates the presence of a PD. In this section III, we shift from defining ten PDs to six, of which three could be framed within the externalizing dimension (namely, narcissistic, antisocial, and borderline, as well as a trait-specified PD in the manner of PD not otherwise specified). While section III of the DSM-5 specifies which facets would indicate the presence of a PD, it does not unequivocally state the pathology threshold for each of the facets assessed. The combined assessment of criterion A and criterion B establishes the presence of PD and profile typology, respectively.

ICD-11 also eliminates the categorical diagnoses of PD, incorporating a continuous measure based on the assessment of personality domains. Like the DSM-5's AMPD, ICD-11 PD is operationalized according to two measures: A measure of personality functioning (severity of personality dysfunction) and another measure characterized by five general traits or domains. The combination of these two measures establishes the presence of the disorder. From a metric perspective, the measure of personality functioning (criterion A: Level of personality functioning for DSM-5 and severity of personality dysfunction for ICD-11) aims at establishing a threshold to differentiate normality from psychopathology. According to DSM-5, criterion A is operationalized according to two broad dimensions: self (identity and self-direction) and interpersonal functioning (empathy and intimacy). ICD-11, on the other hand, incorporates a functioning criterion focusing on harm to others and occupational roles to establish the diagnosis of PD on a continuum of severity[16]. Including the functioning measure in both models is conceptually significant, implying that the presence of an extreme trait would not necessarily be

pathological if dysfunction is not identified.

Similarities are also found in the operational definition of traits/domains offered by the ICD and DSM dimensional personality models. Both models identify five major domains, of which they share four in common. While the AMPD defines the domains of negative affect, detachment, antagonism, disinhibition, and psychoticism, the ICD-11 defines the domains of negative affectivity, detachment, dissociality, dishinibition, and anankastia. However, there are also differences between the two systems. The AMPD operationalizes its dimensions into 25 facets and traits, the combination of which generates personality profiles defining the disorders. However, the ICD-11 considered that this information added unnecessary complexity to the classification[62], so the definition is operationalized at the level of dimensions but not facets. These differences have implications from a metric point of view. Thus, tests from the AMPD model offer a measure of the domains based on the 25 facets to define the disorders. In contrast, those tests that assess according to the ICD model offer only an interpretable measure of the domains. Consequently, the degree of operationalization for test design is greater when applying the DSM-5 AMPD model than the dimensional diagnostic model arising from the ICD-11.

Concerning these models, it should be noted that despite the distinction between the measurement of the level of functioning and the measurement of the traits/domains, the specialized literature has revealed the controversy generated by this distinction. On the one hand, some authors point to an overlap between these two criteria, assuming that assessing pathological traits and facets is an implicit measure of pathological functioning[63,64]. Indeed, psychometric studies based on factor analyses indicate that measures of criterion A and criterion B cluster into common factors when both measures are included in factor analysis[64,65]. On the other hand, this overlap is explained based on the high correlations between dysfunction and pathological traits. Along these lines, some authors argue that the four lower dimensions of criterion A (identity, self-direction, intimacy, and empathy) were conceptualized as indicators of the general dimension of dysfunction[66] and therefore, only one general measure could be used.

On the other hand, the empirical results show a distinction concerning how each criterion A subdimensions are grouped with certain criterion B domains. Specifically, measures of self-functioning are grouped with the negative affect and detachment domains, while measures of interpersonal functioning load on the same factors as measures from the disinhibition and antagonism[63,67,68] domains. Thus, the overlap could be a manifestation of how PTs are expressed and associated with a continuum of severity and how this severity could have a greater impact on an interpersonal or self domain[66,69].

Operational definition of externalizing behavior proposed by HiTOP

The delineation of diagnoses based on diagnostic systems has raised several criticisms[30,70]. Such criticisms include the possibility that the high comorbidity observed between some disorders could reflect, from a metric point of view, a lack of specificity in the diagnostic criteria. This lack of specificity could impact tests based on these classification systems. In addition, the low diagnostic reliability of various diagnostic categories has been highlighted along with the arbitrary nature of the thresholds established to determine a behavior or pathological trait[71,72]. These criticisms are coupled with neurobiological evidence showing that psychopathology is not distinct from normality[30,73,74].

Consequently, other models and taxonomies are emerging that address psychopathology in a cohesive manner, encompassing externalizing personality and behavioral disorders. Possibly one of the most widely supported theoretical models is the HiTOP[17]. This model has introduced several changes: (1) It proposes a hierarchical structure of psychopathology; (2) It adopts a dimensional definition of symptoms, facets, and disorders; and (3) It integrates personality and psychopathology into a single model. The implications of these changes concerning test design are discussed below.

First, the HiTOP[17] defines a general psychopathology framework through a hierarchical structure. Thus, the model specifies (at the lowest level) a set of symptoms and components (*e.g.*, hostility, inattention). These are grouped into syndromes and disorders at the middle level of the hierarchy (*e.g.*, substance use disorder, antisocial PD) and, in turn, are organized into higher structures or spectra (*e.g.*, externalizing spectrum, internalizing spectrum) - that encompass disorders with a common etiology. Finally, at the top level of the hierarchy, a general psychopathology factor (p-factor) is defined that groups the remaining spectra (internalizing, externalizing, and thought disorder)[17]. This hierarchical structure aims to reflect the possibility that different disorders may have common etiological factors[73,75-77]. Therefore, the definition of higher levels is intended to provide an explanatory framework for the co-occurrence of disorders by grouping those disorders with higher co-occurrence into a single factor.

This conceptual advantage poses, however, some challenges in relation to the development of instruments within this approach. On the one hand, the grouping of lower-level facets and symptoms into general factors through a bottom-up approach has been developed on the basis of existing structural evidence in the literature, such as that obtained regarding the AMPD. This evidence, however, is inconsistent[78,79] with certain facets being interstitial (located in more than one domain) and others located in the wrong domain (facets with factor loadings in domains not defined in the models). Moreover, these inconsistent findings have also been noted in other parts of the model[80,81] making it difficult to translate them into a unified operational definition. Moreover, it is also important

to note that the hierarchical structure of the HiTOP implicitly assumes that higher-level latent factors (*e.g.*, internalizing) are the cause of covariation between lower-level symptoms (*e.g.*, fatigue, anhedonia), but the model is unable to represent direct relationships between lower-order elements (*e.g.*, fatigue may lead directly to anhedonia)[82]. These relationships, for example, are better captured through newly emerging network models[83,84]. Finally, it is important to determine at which level of the hierarchy operationalization occurs so that assessment of different components of the same level shows equivalent specificity or generality[85].

The second element of HiTOP with implications for the measurement of disorders is related to the conceptualization of disorders as a continuum from normality to pathology and defines a set of dimensions at all levels of the hierarchy. This dimensionality at the lower levels allows us to account for the variability of patients within the same disorder[30,86] and simultaneously aims to solve the problem of arbitrariness in the pathological thresholds. From a measurement perspective, adopting a dimensional approach increases the reliability of the measure and is shown to be a better model for explaining and predicting the chronicity of disorders[82]. However, this element also poses some measurement challenges. On the one hand, such a model is intended to be applied in the clinical setting and thus should facilitate clinicians' decision-making regarding administration of treatments or determining the time of discharge. On the other hand, for these decision-making processes, there is still a need to establish cutoff points to assist clinicians. According to the authors of the model, while diagnosis is oriented toward profiling the severity of a patient's symptoms, these thresholds can be established according to empirical evidence[28]. Although these cutoff points have begun to be defined for some parts of the model[87] many other parts still lack such guidance. Another alternative for interpreting HiTOP-compliant measure scores is to use normative data that transforms a patient's score into standardized scores[28]. However, it should be noted that many studies have been conducted with community samples, thus excluding those scores that fall within the pathological range. When interpreting a patient's score, this could be problematic.

The third relevant aspect of HiTOP for the operational definition of disorders concerns the integration of available structural evidence on psychopathology and personality[28,86,88-90]. Thus, personality and conduct disorders would fall under the same explanatory framework, eliminating the differentiation between personality and psychopathology. However, this aspect could be problematic, considering the time frame used for assessing symptoms and signs[90]. While personality facets (*e.g.*, Callousness) are conceptualized as stable characteristics and traditionally include broad assessment timeframes, behaviors or symptoms are understood as evidence of a person's one-off state (*e.g.*, Substance use, assessed with a shorter timeframe). Grouping personality facets and behaviors in the same model is challenging when assessing different time frames. This is especially relevant as different spectrums of the HiTOP taxonomy would be operationally defined to a greater extent by symptoms, while for others this is traits or a combination of both[85].

Concerning the structure of the externalizing spectrum, the HiTOP model, in its original version[17] proposes a definition according to two separate dimensions: Antagonistic externalizing and disinhibited externalizing. While the former includes aggressive traits and behaviors (especially in interpersonal contexts), disinhibited externalizing groups together traits and behaviors that manifest difficulty in controlling impulses. The operationalization of the externalizing spectrum in these two dimensions is supported by the replication of this structure in several previous models, albeit with different descriptive labels[91-93]. In addition, after the publication of HiTOP, this structure has received support from factor analyses and meta-analyses[89,94]. Furthermore, according to the model, taken together, these two dimensions - externalizing antagonism and disinhibition - contribute toward explaining antisocial and aggressive behavior[90].

The authors proposing HiTOP have worked along two lines concerning measurement. On the one hand, they have provided a list of previously available instruments that offer a HiTOP-compatible measure[17,85]. Within the externalizing spectrum, the Externalizing Spectrum Inventory (ESI)[74] stands out among the recommended instruments, as this instrument provides the most comprehensive - although not complete - measure of the two dimensions of the externalizing spectrum. On the other hand, the Measures Development Workgroup of the HiTOP is currently developing instruments specifically designed according to the model. Unfortunately, no measure is yet available, although Mullins-Sweatt *et al*[90] reviewed the externalizing facets that serve as an operational definition for a proposed externalizing spectrum measurement instrument.

INSTRUMENTS FOR MEASURING DISINHIBITED AND ANTAGONISTIC EXTERNALIZING DISORDERS

It has previously been shown that there are various ways of operationalizing the externalizing constructs associated with the problem behaviors that are central to this study, focusing on nosotaxias and HiTOP as the most valid classification systems. However, a specialized literature review shows that there are still more existing measurement instruments for externalizing problem behaviors. After reviewing these instruments, we would like to point out several aspects. First, many published tests and

scales do not clarify the underlying operational definitions. This inadequacy may be due to the authors' negligence or aspects associated with editorial policies. In either case, failure to specify operational definitions results in a lack of specificity regarding the measured constructs. Another aspect that the authors noted in their review was the inconsistent use between the application of the psychometric techniques and the evidence they intended to provide. For example, there is an indiscriminate use of the factor analysis technique (in its exploratory, confirmatory, or exploratory structural equation modeling variants) to determine the structure of an instrument without conceptually delimiting the underlying theoretical structure. Consequently, we have observed how authors eliminate items with factor loadings below a specific arbitrary threshold[95,96], correlate item errors to improve fit indexes[97-99], or establish cross-loading without reflecting on the impact on the test content validity[99]. Finally, we would like to warn that the availability of a large number of tests, as is currently observed, most likely results in atomization in the measurement of these constructs, which is counterproductive for making progress in acquiring knowledge of these mental disorders. Given this, efforts should focus on targeting fewer instruments that are rigorously developed and versatile in their applications.

The following is a brief description of various interviews and tests available in the specialized literature that allow the measurement of externalizing problem behaviors. The selected instruments listed respond to their impact concerning their use in scientific publications and their clinical interest. Moreover, considering the large amount of psychometric evidence available, the authors have chosen to describe only and exclusively those metric aspects most directly associated with their underlying operational definition.

Instruments with diagnostic targets developed from the DSM and ICD

Diagnostic interviews to assess different disorders: Instruments that make clinical diagnoses are usually based on the DSM and ICD nosotaxias. Therefore, these diagnostic classifications form the basis for the operational definitions of these tests. These instruments provide a categorical scoring system that determines the absence or presence of a disorder. They are usually structured or semi-structured interviews whose items largely reproduce the wording of the diagnostic criteria that appear in the above nosotaxias. These items are often accompanied by clarifications to assist clinicians in the scoring process.

For the most part, changes in the diagnostic criteria of the different versions of the ICD and DSM have been reflected in updated versions of these structured and semi-structured interviews through modifications to their items. Considering the diffusion in their administration, the main structured clinical interviews that measure mental disorders - and therefore include externalizing disorders associated with problem behaviors - are the SCID-5[20,21] the CIDI[22], the Mini International Neuropsychiatric Interview (MINI)[100], Psychiatric Research Interview for substance and mental disorders (PRISM)[101] and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[102]. However, there are differences between these interviews. The SCID, PRISM, and MINI interviews use the DSM diagnostic criteria to diagnose disorders, while CIDI and SCAN allow diagnosis from both nosotaxias. Moreover, there are also differences in the level of structuring of the interviews. This is why the skill level of those administering the interviews is relevant for obtaining reliable and valid diagnoses - the less structured the interview, the greater the need for interviewers to be adequately trained.

The SCID is an interview that highlights the distinction between the assessment of psychopathological disorders and PDs, publishing separate versions for both disorders[19-21]: SCID-I for DSM-IV Axis I disorders and SCID-II for DSM-IV Axis II. The changes introduced in the DSM-5 have been transferred to this diagnostic interview, developing the SCID-5-CV for psychopathological disorders and the SCID-PD for PDs. Concerning the disorders of concern in the present work, the SCID-5-CV is administered to assess substance use disorder and ADHD. The SCID-5-PD is administered to measure histrionic, narcissistic, borderline, and antisocial PD.

The CIDI[22] is an interview developed by the World Health Organization which has subsequently been updated[103,104], giving rise to the different versions of this structured interview. From a metric perspective, the latest version of this interview provides an evaluation according to DSM-IV and ICD-10 criteria. However, its items are not a translation of the diagnostic criteria of the nosotaxias. Among its distinctive features, it should be noted that this interview includes questions on general health followed by those associated with the diagnosis. These questions are designed to provide a screening tool that reduces the administration time of the instrument and limit interviewee fatigue, thus improving the validity of the information obtained. It also includes scales on clinical severity and impairment to determine whether the symptoms experienced by respondents produce clinically relevant distress.

The MINI is a structured interview aimed at screening for the presence of disorders[100]. It primarily focuses on measuring internalizing disorders. Among the externalizing antagonistic and disinhibiting disorders, the MINI plus version includes the assessment of substance use disorder, ADHD, and antisocial PD. The latest version of the MINI adapted to DSM-5 (MINI-7.0.2) does not include the assessment of ADHD. For measuring the disorders, the items of this interview are worded very similarly to the DSM-5 diagnostic criteria and its scoring system also reproduces that indicated in the DSM-5 for each disorder. Due to the lack of in-depth exploration of the possible presence of mental disorders, the MINI is considered primarily a screening interview.

The PRISM is a semi-structured interview designed to improve the reliability and diagnostic validity of psychiatric disorders in patients with substance use disorder[101]. This is because these patients mimic numerous symptoms present in other mental disorders[105]. Therefore, providing an instrument to identify when mental disorders are primary and induced by substance use was considered relevant. From a psychometric perspective, therefore, this interview aims to provide high specificity in diagnosing the disorders assessed. However, due to the detailed exploration involved in this interview, its duration is long. For this reason, computerized versions have been developed to reduce administration time. There is currently a version of the PRISM adapted to the DSM-5[106].

Substance use disorder specific assessment instruments: The assessment of substance use disorders based on the diagnostic systems is mainly achieved through the diagnostic interviews mentioned above. In addition to these, other diagnostic interviews and scales specific to substance use disorder have been shown to be useful for diagnosis.

The Substance Dependence Severity Scale (SDSS)[107,108] is a semi-structured diagnostic interview specifically used for substance use, whose items allow a diagnostic assessment according to DSM-IV and ICD-10 criteria. A Spanish version evaluates substance use disorder according to DSM-5[109,110]. This instrument consists of 16 items that operationalize the 11 diagnostic criteria proposed in the DSM-5. The items of the SDSS can be sectioned into two parts: A screening section and another section that assesses the severity of the substance use disorder. One of the characteristics of this interview is that, although it is guided by diagnostic criteria, it conducts the assessment using a time frame of the previous month, as opposed to the last 12 months used by the classification systems. This time frame is motivated by the search for the sensitivity of the scores to detect changes in patients[107,108]. To be congruent with making the diagnosis according to DSM criteria and to make the scores sensitive to changes in patients, a scoring system has been designed which is compatible with the DSM diagnostic procedure, which, in addition, provides a continuous score.

Problems associated with substance use have also been assessed employing other instruments which, although based on the diagnostic criteria of nosotaxias, do not pursue a diagnostic purpose as such. One such instrument is the Severity Dependence Scale[11]. This brief 5-item self-administered scale provides a severity score for drug dependence and is designed to measure the psychological aspects of dependence experienced by drug users. To this end, its items focus on measuring compulsive drug use, the individual's worry and anxiety about their own drug use, and feelings of impaired control over their drug use. Thus, although its items are based on the diagnostic criteria for nosotaxias, not all diagnostic criteria are operationalized in this instrument. This scale has been studied by adapting it to different drugs, and studies have confirmed its psychometric properties in users of heroin, cocaine, and amphetamine[11] alcohol[111], marijuana[112,113] ketamine[114] and codeine[115]. The Short Alcohol Dependence Data Questionnaire[116] assesses the severity of alcohol use disorder through 15 self-administered items. These items focus on measuring drinking habits and the physical and mental effects of drinking. Another scale that allows an assessment of alcohol consumption is the Severity of Dependence Questionnaire (SADQ)[117]. The current form of the SADQ is a 20-item questionnaire that assesses physical signs of withdrawal, affective signs of withdrawal, craving, quantity, frequency of drinking, and the speed of recovery from withdrawal symptoms. The Alcohol Use Disorders Identification Test[118] is a specific screening test for detecting problematic alcohol use. Its items operationalize some of the diagnostic criteria for nosotaxies, and due to its simplicity, this instrument is widely used in clinical and research settings.

Specific ADHD assessment instruments: Most instruments that assess ADHD are based on the diagnostic criteria for nosotaxies. However, some differences between them are worth noting. The following describes the most commonly used instruments and their main characteristics under a psychometric approach.

The Adult ADHD Self Report Scale (ASRS)[119,120] is a screening scale that operationalizes the diagnostic criteria proposed in the DSM-IV through 18 items. It also offers three types of scores (inattention score, hyperactivity score, and total score) according to the clinical signs of ADHD. It is, therefore, a scale that largely reflects the diagnostic procedure based on nosotaxies. However, its items do not explore the presence of the disorder in depth, and it is thus considered more of a screening than a diagnostic instrument.

The Current Symptoms Scales[121] is an 18-item instrument that can be completed by an observer (CSS-OR) and/or self-administered (CSS-SR). The 18 items describe the DSM-IV diagnostic criteria included in the inattention and hyperactivity/impulsivity domains. In addition, this instrument differs from others in that it includes a scale to assess the intensity with which the symptoms interfere with the individual's functioning in various areas of their life (work, family life, or money management).

The Connors Adult ADHD Rating Scale (CAARS)[122] is available in different versions (large version: 66 items, short version: 26 items, and screening version: 30 items), with two main formats: One self-report and one observational (CAARS-SR and CAARS-OR, respectively). This scale uses items based on - but not exclusively guided by - diagnostic classifications. Thus, it offers more items to explore inattention, hyperactivity, impulsivity, or self-concept. In addition, an index of the probable presence of ADHD can be derived from its scores along with indicators of the inconsistency of responses.

The WURS[13,14] is a scale that retrospectively assesses ADHD symptoms in childhood. This scale has two versions (the original version with 61 items and the short version with 25 items). This scale generates scores for hyperactivity, attention deficit, and impulsivity, along with emotional lability and behavior problems. The contents of this scale are based on the Utah criteria. Thus, while the WURS does not assess the criteria for nosotaxies *per se*, its cutoff scores (36 and 46) have shown to be useful for diagnostic categorization.

Specific instruments for the assessment of personality domains: The shift towards the definition of disorders based on personality traits has led to the emergence of various instruments aligned with this theoretical premise. The present study will characterize psychometrically those instruments that assess the dimensions of the externalizing spectrum underpinning the disorders associated with behavior problems corresponding to the antagonism and disinhibition domains of the DSM-5 and aligned with the dissociality and disinhibition domains, respectively, of the ICD-11[123]. Furthermore, among the existing instruments, the present study will analyze those that are most widely used, such as the Personality Inventory for DSM-5-PID-5-[33] and the Personality Inventory for ICD-11 (PiCD)[124].

The PID-5[33,34] assesses 25 facets/traits proposed in the AMPD, including those for disinhibition and antagonism. The original version of this instrument includes 220 items. Subsequently, other reduced versions of 100 items (PID-5-SBF)[125] and 25 items[126] have been published. This latest version (PID-BF) only provides a score for the domains. This instrument has been adapted to numerous languages[127-133], with considerable psychometric evidence. Thus, the review conducted by Al-Dajani *et al*[134] showed, in terms of reliability, alpha values ranging between 0.72 and 0.96. Regarding test-retest reliability, values above 0.90 have been reported for all dimensions. In terms of validity evidence based on the relationship with other variables, it has been found that the structure of the PID-5 converges with the FFM model[135]. Correlations above 0.60 have been reported in the convergence between disinhibition and antagonism with their respective counterparts in the NEO-PI-R and NEO-PI-3[67,136-138]. Regarding the factor structure, most factor analyses show that the factor for externalizing divided into two sub-factors is congruent with the domains of externalizing and disinhibition. It should be noted that this instrument allows the identification of personality traits and facets, and some authors have subsequently analyzed the congruence of these profiles with the categorical diagnoses of nosotaxies[69,67,129,139].

The PiCD[124] has been developed to measure the dimensional personality model proposed by the ICD. The PiCD assesses the five domains proposed by ICD-11, including the three specific externalizing domains of dissociality, disinhibition, and anankastia traits. This instrument includes 60 items, so the five domains are assessed based on 12 items each. Psychometric studies of the PiCD have shown adequate internal consistency coefficients[124,139-143]. Concerning evidence of convergent validity, PiCD scores have shown significant relationships with their counterparts in other personality models [140-142,144]. In the case of the disinhibition and dissocial dimensions, high correlations have been found with their convergent scales but not with scores measuring anankastia[140]. Regarding the factor structure, some studies replicate the five proposed theoretical factors[62,124,145], while other authors point to an overlap between the disinhibition and anankastia factors[140,144]. Although PiCD proposes a primarily domain-based measure congruent with DSM-5, Bach *et al*[146] developed scoring algorithms for the ICD-11 facets based on the PID-5 dimensions, finding a good fit for the disinhibition, antagonism/dissocial, and anankastia dimensions. These results have subsequently been replicated in other studies[147,148].

Instruments for assessing the antagonism and disinhibition externalizing domains compatible with other psychopathological models

In addition to the instruments mentioned above, other tests and scales allow the assessment of the traits included in the externalizing antagonistic and disinhibition domains that do not adopt the DSM and ICD classifications as a basis for operational definition. The items of these instruments do not tend to reproduce the diagnostic criteria of nosotaxies. Rather, their items are organized for the measurement of traits and facets, usually on a severity scale, which is indicative of the presence of problem behaviors or disorders.

On the other hand, it should be noted that numerous instruments measure each of the antagonistic and disinhibited problem behaviors. However, in the present work, we will incorporate instruments that measure more than one of these problem behaviors or disorders. In this regard, it should be noted that, as Mullins-Sweatt *et al*[90] reported, an instrument is currently being developed to measure problem behaviors and disorders within the externalizing spectrum.

One of the instruments worthy of note is the Achenbach System of Empirically Based Assessment (ASEBA)[149]. This assessment system integrates instruments for measuring various behaviors, competencies, and interpersonal problems. Its objective is concerned with detecting problematic behaviors that can be the object of clinical intervention, although it distances itself from the use of diagnostic categories proposed in the nosotaxies. This assessment system can identify profiles concerning various behaviors, including those framed within the externalizing spectrum. Its scales include the ASR and the Adult Checklist[150,151], which report on adaptive and problematic behaviors, including drug use.

The MMPI was originally developed by Hathaway & McKinley[152,153], and the third version (MMPI-3)[154] has been recently published. In its three updates, this instrument retains the aim of providing assessors with a clinical profile that contributes to the characterization of individuals in a comprehensive manner. Therefore, its different versions include many scales that are organized to provide trait and behavioral scores while providing scores from high-order scales, including specific scores associated with the antagonism and disinhibition domains.

The PAI[26,27] is another instrument that assesses various personality traits and facets, including the disinhibition and antagonism domains. It is an instrument whose aim is not only to provide clinically relevant information for diagnosis but also useful information for planning the treatment of patients. In this sense, the authors selected those syndromes that, at the time of their development, had the greatest relevance in the nosology of psychopathology and usefulness in clinical practice. In turn, the operational definition of these syndromes was based on a review of the specialized literature to identify the most central components. Subsequent versions of the PAI have included new scales that currently measure a wide range of behaviors and traits that allow for establishing detailed profiles of the persons assessed.

Krueger *et al*[74] developed the ESI to test a comprehensive model of externalizing disorders. To this end, the authors reviewed the literature and focused on how certain disorders (*i.e.*, substance use disorders or antisocial behavior disorders) could have common etiological bases and, therefore, should be integrated into the same continuum. Under this premise, the authors developed the ESI to provide scores for personality and behavioral domains based not on phenotypic manifestations but on the underlying common structure of these domains. From here, to develop the items the authors adopted/modified items from existing measurement scales, and also designed items based on the DSM-IV-TR diagnostic criteria.

INTEGRATION PROPOSAL

For years, several authors have postulated the need for integrative models based on the classic DSM and ICD approaches combined with other empirical models that address the underlying bases of the different disorders[155,44]. This approach is, for example, followed by the AMPD or the ICD for PDs. While recognizing the value and interest of these efforts, it should not be overlooked that moving from a model with categories that determine the presence or absence of a disorder to one in which profiles are developed to identify traits and facets with normal/pathological functioning, implies a considerable leap. Consequently, many clinicians may be unable to determine which clinical and pharmacological interventions are most appropriate for their patients. Likewise, considering the nature of the disorders addressed in this paper, professionals in the judicial and educational fields (among others) must become familiar with these new approaches to make the right decisions. However, the existing empirical evidence[30,31,70] and the promising results obtained in clinical settings with transdiagnostic interventions[156,157] suggest the need to adopt these new models.

As our review has shown, while efforts have been made to bring nosotaxies together with other theoretical models of psychopathology and personality, these have not played a prominent role in practice. However, nowadays, with the major development of models such as HiTOP, we may be moving closer to achieving convergence between these approaches, and to this end, tests and scales may play a central role.

Our research group is currently developing an instrument to measure the variable 'Externalizing disorder in adulthood' with the aim of constructing a test to identify profiles along the Agreeableness-Antagonism and Conscientiousness-Disinhibition continuums. In addition, our objective is to develop items that constitute indicators that can be used to determine the presence (or absence) of externalizing disorders according to DSM-5. Thus, the framework underpinning the operational definition of the test will be the HiTOP model[17,90] and the DSM-5 diagnostic criteria[15] and in the latter case, integrating the proposals of the alternative personality model and the diagnostic criteria of section II.

Our proposal begins with the definition of 'Externalizing disorder in adulthood' as "a set of maladaptive and/or problematic behaviors and personality traits that manifest themselves through outwardly directed behaviors, which cause deterioration in social relationships and interfere with the normal functioning of the person who presents them and their environment". This construct, congruent with that stipulated in the HiTOP, presents a hierarchical structure that integrates two major dimensions: Antagonism and disinhibition, divided into facets and traits. The disorders to be integrated are antisocial, narcissistic, paranoid, borderline, histrionic, ADHD, and oppositional defiant disorder. Substance use disorder, intermittent explosive disorder, and conduct disorder are not included for several reasons: (1) Concerning substance use disorder, there is abundant specialized literature showing that although it falls within the antagonism and disinhibition domains, these always clearly form an independent factor[158,159]. This means that some of the existing scales[107-109] can currently be used for their without disrupting the assessment of these two domains; (2) Explosive-intermittent disorder is not included due to the difficulty in identifying clear diagnostic criteria. Specifically, the DSM-5 only offers a list of behaviors or problems that must be present, although it does not define any criteria to determine their presence/absence; and (3) Conduct disorder is not included due to the lack of

adaptation of the set of diagnostic criteria to the adult population.

The DSM-5 definitions of facets and traits and those proposed by Mullins-Sweatt *et al*[90] have been adopted to delineate the operational definition. However, as indicated, our proposal integrates facets and traits with the criteria specified in section II of the DSM-5. In this sense, the research team members have reviewed the specialized literature to reach the proposal shown in Table 1. This table shows, for example, that the diagnostic criteria for antisocial PD fall within the two dimensions of our model: Five of the seven criteria refer to facets of disinhibition, and two of them to antagonism. For example, criterion 6, "Consistent irresponsibility, manifested by repeated inability to maintain consistent work behavior or meet financial obligations" corresponds to "Irresponsibility". It is therefore proposed that in the final version of the test, within the items measuring this facet, there should be items whose content deals with this diagnostic criterion.

Establishing equivalence between facets/traits and diagnostic criteria provides a conceptually equivalent operational definition. Thus, the test resulting from this definition may be of interest to professionals in various fields. First, quantitative data can be obtained to locate people along different continuums of facets, dimensions, and the externalizing spectrum. From a research standpoint, it will be possible to verify the hierarchical structure of externalizing behavior problems in the adult population and to analyze, through statistical models, their relationships with other variables of interest. Second, regarding clinical application, professionals will be offered equivalence scores that will allow them to determine the presence/absence of a given diagnostic criterion and, taking into account the relevant diagnostic criteria, the existence (or not) of the corresponding PD. The operational definition provided in present manuscript is a preliminary approach that attempts to combine the theoretical advances, result of the most recent empirical research, with the clinical practice, based on the nosotaxies internationally used.

CONCLUSION

Present work highlights the importance of that measurement of externalizing spectrum disorders has for people's living conditions[3-7]. The development of measurement instruments for these disorders requires a careful process of design, application, and interpretation[8]. The bibliographic review undergone show that among the available instruments, there are those framed within categorical diagnostic systems (DSM and ICD); those arising from recent dimensional theoretical approaches (AMPD or HiTOP) and other instruments with operational definitions in specific theoretical frameworks. While categorical approaches provide useful tools to facilitate clinical decision-making, dimensional approaches have extensive empirical support as better capturing the nature of the disorders and allow greater understanding of psychopathological phenomena[28].

On one hand, our review note that the different operational definitions used in these tests under the different frameworks, hinder the comparison of the findings and applicability. Regarding the definitions based on diagnostic classification systems, these have undergone an evolution throughout the different editions with three phases. While the first editions constituted mere statistical classification systems, later versions incorporated descriptions of diagnostic categories[9,10], providing the first operational definitions of psychological disorders in general and externalizing disorders in particular.

The development of measuring instruments for these disorders did not, therefore, truly flourish until diagnostic criteria were included on these taxonomies[43] on a second phase. The inclusion of these criteria lead to a tendency towards quantifying disorders through tests, rating scales, and checklists. In addition, the criterion of dysfunction to consider the presence of a disorder were incorporated into these taxonomies[50], which led to the development of new measures for the assessment of impairment[53-57]. However, while systematization in assessment increased, many of the instruments developed from this perspective have been criticized for lacking an etiological theoretical framework[45,49]. Also, the differentiation between Axis I (substance use and impulse control disorders) and Axis II (PDs) on these classification systems[52,58], caused that tests based on nosotaxies either assess symptoms (psychopathology) or traits (personality).

The assessment of disorders based on these categorical classifications in this second phase, has been criticized in a number of ways[30,70]. Criticisms included the observation of high rates of comorbidity - due to the lack of specificity of diagnostic criteria - and the arbitrary nature of the thresholds between normal and pathological behavior[71,72]. On the third phase of evolution of diagnostic classifications, latest versions of DSM and ICD had begun a shift towards a dimensional operationalization of mental disorders. The AMPD model included in DSM-5 Section III[15] and the ICD-11[16] constitute two first proposals for a dimensional classification of PDs. Again, it can be noted that the measurement of functioning play a relevant role on these proposals for defining the threshold that differentiate normality from pathology. However, empirical evidence show mixed results regarding the overlap when measuring functioning and pathological traits[64-69].

In addition to the operational definition of externalizing disorders provided in the different taxonomies, our review analyzed another recent dimensional model: The HiTOP model[17]. This recent dimensional model had provided an extended classification system that address all types of psycho-

Table 1 Relationship between diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders-5) and externalizing facets-dimensions

Externalizing disorders in adulthood			Internalizing
DSM-5 disorders (diagnostic criteria)	**Disinhibition**	**Antagonism**	
Antisocial [Personality disorder, diagnostic criteria section II (3/7)]	Non-compliance with standards (criterion 1)	Deception/fraud (criterion 2)	
	Impulsivity (criterion 3)	(Lack of) empathy (criterion 7)	
	Aggression (physical) (criterion 4)		
	Risk-taking (criterion 5)		
	Irresponsibility (criterion 6)		
Narcissistic personality disorder [Diagnostic criteria (5/9)]		Grandiosity (criteria 1, 2, 3, 5, 8, and 9)	
		Attention seeking (criterion 4)	
		Exploitation (criterion 6)	
		(Lack of) empathy (criterion 7)	
Paranoid personality disorder [Diagnostic criteria (4/7)]		Mistrust (criteria 1-4, and 7)	
		Hostility (criteria 5 and 6)	
Borderline personality disorder [Diagnostic criteria (5/9)]			Separation anxiety (criterion 1)
			Affective lability (criteria 2 and 6)
			Altered self-perception (criterion 3)
	Risk-taking (criterion 4)		
			Suicide (criterion 5)
			Depression (criterion 7)
		Hostility (criterion 8)	
			Dissociation (criterion 9)
Histrionic personality disorder [Diagnostic criteria (5/8)]		Attention seeking (criteria 1, 2, 4, and 6)	
			Affective lability (criterion 3)
			Superficiality (criterion 5)
			Suggestibility (criterion 7)
			Altered social perception (criterion 8)
ADHD [Inattention (5/9)]	Inattention (criteria a-i)		
Hyperactivity and impulsivity (5/9)	Hyperactivity (criteria a-f)		
	Impulsivity (criteria g-i)		
Oppositional defiant disorder [Diagnostic criteria (4/8)]		Hostility (criteria 1-3 and 8)	
		Rebellion (criteria 4-7)	

DSM: Diagnostic and Statistical Manual of Mental Disorders.

pathology. Regarding externalizing disorders, it provides a coherent theoretical background for explaining comorbidity through the definition of general factors - Antagonistic externalizing and Disinhibited externalizing, grouped in the Externalizing spectrum - that group co-occurring symptoms. This hierarchical structure however, is not clearly supported by empirical evidence[78-81], appear to ignore the direct relations between the lower level elements[82-84], and provide challenges on the operational definition under the different levels of the model. The dimensional conceptualization increases the reliability of the measure, although requires to establish empirical based cutoff points to

assist clinicians[82]. Finally, considering HiTOP model gather personality and conduct disorders, measuring sign and traits under the same instrument can pose differences on the time frame of assessment.

On the other hand, the review of existing instruments for measuring externalizing disorders have shown a large amount of test, resulting in an atomization in the measurement. This implies that researchers and practicioners should carefully revise the operational definition and target of each instrument to ensure a good choice of measurement instrument for a specific purpose, although our review show that this information may be of difficult access or not clear. Among the structured interviews developed under the classification systems, it is worth mentioning the SCID-5[20,21], the MINI[95], and the PRISM[96] under the DSM framework and the CIDI[22], and the SCAN[97] allowing diagnosis under both DSM and CIE taxonomies. Less structured interviews such as the PRISM or the CIDI, require interviewers to be adequately trained. Regarding instrument for assessing specific disorders, our review suggests the ASRS[119,120], the Current Symptoms Scales[121], the CAARS[122] within the DSM criteria and the WURS[13,14] based on the Utah criteria are the most frequent measurement instruments. On personality, due to the emergence of dimensional personality models, it can be found measurement instruments within dimensional frameworks such as the PID-5[33,34], the NEO-PI-R, NEO-P-3[67,136-138] and PiCD[124]. Other dimensional instruments targeted to measure antagonism and disinhibition include the ASEBA[149], MMPI[152-154], the PAI[26,27] and the ESI[74].

Present review show that the different instruments identified are either designed under a diagnostic taxonomy framework which allow a categorization of the respondents or under theoretical framework derived from research that delineate dimensional profiles. As our review suggests, efforts to bring nosotaxies together with other theoretical models have not played a prominent role in practice. We provide a preliminary operational definition that attempts to combine both approaches.

FOOTNOTES

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REVIEW

Psychiatrists' occupational stigma conceptualization, measurement, and intervention: A literature review

Xiao-Li Shi, Lu-Yao Li, Zhi-Guang Fan

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Abstract

Psychiatrists require frequent contact with and treatment of patients with mental illnesses. Due to the influence of associative stigma, psychiatrists may also be targets of stigma. Occupational stigma warrants special consideration because it significantly affects psychiatrists' career advancement, well-being, and their patients' health. Given that there is no complete summary of this issue, this study reviewed the existing literature on psychiatrists' occupational stigma to clearly synthesize its concepts, measurement tools, and intervention strategies. Herein, we emphasize that psychiatrists' occupational stigma is a multifaceted concept that simultaneously encompasses physically, socially, and morally tainted aspects. Currently, standardized methods to specifically measure psychiatrists' occupational stigma are lacking. Interventions for psychiatrists' occupational stigma may consider the use of protest, contact, education, comprehensive and systematic methods, as well as the use of psychotherapeutic approaches. This review provides a theoretical basis for the development of relevant measurement tools and intervention practices. Overall, this review seeks to raise public awareness of psychiatrists' occupational stigma, thereby promoting psychiatric professionalism and reducing its stigma.

Key Words: Psychiatrists; Occupational stigma; Conceptualization; Measurement; Intervention; Associative stigma

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Core Tip: Psychiatrists' occupational stigma, an area that is little noticed, deserves more attention from the public and professionals considering its negative effects. This study aimed to elucidate its concept, explore the potential measurement tools, and focus on effective interventions by comprehensively reviewing related literature. It is expected to encourage more studies in this field.

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INTRODUCTION

Stigma is a form of social classification. Occupational stigma results when people make derogatory, insulting, or negative comments about others practicing their occupation[1]. Occupational stigma is the negative labeling of a profession that the general public views as having dishonorable, humiliating, and shameful features, leading to negative consequences of social exclusion, status loss, demeaning, discrimination, and pessimistic rejection[2-4]. Although stigma arises from dirty work in common sense, any occupation can face various levels and types of stigma[3]. Physicians, a typically prestigious profession [5], also suffer from stigma that seriously jeopardizes health care career development[6,7]. Furthermore, psychiatrists may experience intense stigma due to the nature of their profession and the population they serve[8]. A study of trainee psychiatrists found that 75% of individuals heard denigrating or humiliating remarks about the psychiatric profession[9].

Occupational stigma exerts negative impact on psychiatrists' career advancement, well-being, and patients' health. More specifically, the stigma may cause burnout, job dissatisfaction, and low professional value[10-17], and can act as a strong predictor of health and well-being[18,19]. Numerous studies have demonstrated that occupational stigma contributes to practitioners' withdrawal behaviors and the propensity for resignation[14,20-22]. At present, the shortage of psychiatrists cannot meet the demands of mental health workforce development[23]. Alarmingly, a study suggested that just about half of psychiatry college graduates moved on to work in related disciplines[24]. It has shown that occupational stigma plays a major role in that kind of phenomenon[25-28]. In addition, as a consequence of stigma, medical students rarely consider psychiatry a future career option, with the perception of taking psychiatrists as having low professional prestige and respect[29-31]. The professional shortage in psychiatry has been existing considering the insufficient medical graduates attracted by psychiatry[32, 33].

Moreover, it is noteworthy that stigma can straightly influence the establishment of the well physician-patient relationship and the treatment process. Stigma is classified as either public stigma or self-stigma, in which patients' stigma toward psychiatrists falls under the former[34]. That public stigma can reduce patient compliance and help-seeking behavior, thereby impeding treatment[32,35]. For another, psychiatrists' self-stigma may result in an increase in defensive medical behavior[36], such as little communication with patients, unnecessary testing, excessive medication, refusal, or referral[37-39], leading to not only health-care costs rise and poor medical relationship but also the potential negative impact on patient health and treatment effect[40].

In conclusion, psychiatrists influenced by associative stigma are perceived as a heavily stigmatized profession. Despite numerous studies showing that occupational stigma exerts a significant negative impact on the development of psychiatry, there is little literature reviewing psychiatrists' occupational stigma. To that end, the purpose of this literature review is to provide a comprehensive overview of the concept, measurement, and intervention of psychiatrists' occupational stigma by reviewing the extant literature, with the prospect of providing a theoretical reference for future research.

LITERATURE SEARCH

The authors sequentially searched the PubMed, Web of Science, and Reference Citation Analysis (https://www.referencecitationanalysis.com/) databases for articles containing a cross combination of the following topical keywords: "Psychiatrist," "stigma," "occupational stigma," "stress," "negative affect," "career satisfaction," "dirty work," "healthcare workers," "associative stigma," "psychiatry," "mental health professionals," "self-stigma," "mental illness," "intervention," "measurement," and "anti-stigma." March 2023 was the deadline for the keyword search, which yielded an initial total of 21098 papers. Literature selection criteria, as decided between the professor and students, were as follows: First, include a study relevant to and representative of the topic; second, any such study should be published in English or French; third, exclude duplicates. After review 195 papers met the selection

criteria and 20903 papers were excluded.

CONCEPTUALIZATION OF PSYCHIATRISTS' OCCUPATIONAL STIGMA

Research on occupational stigma can be traced back to Hughes[2] and his exploration of dirty work[2]. Impressive findings have been attained in the following studies that explore occupational stigma across practically all professions[3,41,42]. In his research on dirty work, Hughes[2] classified occupational stigma into three categories: physically, socially, and morally tainted in the aspect of work content[2]. Based on this, Ashforth and Kreiner[43] provided a precise definition of the three different forms of stigma[43]. Particularly, the term "physically tainted" refers to jobs that involve direct contact with trash, death, or filth[44,45] such as cleaner and mortician, or directly working in dangerous and harmful environment[46,47] such as firefighter and miner. The term "socially tainted" describes jobs like prison guards and infectious disease doctors that require regular contact with stigmatized groups as part of their duties[48,49], as well as those like nannies and tour guides that include a servant-subordinate relationship[50,51]. The term "morally tainted" refers to occupations that are viewed as being sinful and unethical[52,53] such as doctor who perform abortions or sex worker, as well as occupations with leading and deceptive traits[54,55] such as anchors who lead viewers to spend money and poker players who deceive their opponents. It is critical to note that one type of stigma may predominate in a given occupation, or two or even three types of stigma may exist concurrently[3,43]. Stenger *et al*[56] extended the three-dimensional classification, arguing that occupational stigma is a negative stereotype formed by the public of certain occupations' work images, social relations, or ethics[56].

In a follow-up study, Kreiner *et al*[3] further proposed the concepts of "breadth" and "depth" of taint applied to work tasks undertaken[3]. Breadth refers to the centrality of stigma in occupational identity, and the frequency of stigma-related behaviors occurring. Depth refers to the degree to which a practitioner is directly exposed to dirt. Accordingly, occupational stigma was further divided into pervasive stigma, compartmentalized stigma, diluted stigma and idiosyncratic stigma. At the same time, Ashforth and Kreiner[42] took occupational reputation as an important dimension of occupational stigma division, and then divided occupational stigma into high/low reputation physically tainted, high/low reputation socially tainted, and high/low reputation morally tainted[42]. In a recent study, Zhang *et al* [57] analyzed the four-level stigma literature of individual, occupational, organizational, and industry, and divided the sources of stigma into six types (physical, tribal, moral, servile, emotional, associational), which extended the three-dimensional classification of occupational stigma. The sources of occupational stigma are considered to include these six types. At the same time, five characteristics of stigma (concealability, controllability, centrality, disruptiveness, malleability) are further proposed. Scholars believe that the types of stigma source and the characteristics of stigma under different social conditions will jointly influence the formation of stigma[57].

At present, different scholars do not consistently agree on the concept of occupational stigma. The above-mentioned concepts of stigma proposed by Hughes[2], Ashforth and Kreine[41] are most commonly used in related studies. To this end, this study also defines the concept of occupational stigma toward psychiatrists in the aspect of physical, social and moral, and explores the specific causes of occupational stigma.

People with mental illnesses are frequently labeled as "violent," "offensive," "dangerous," and "aggressive"[58]. Compared to doctors in other clinical departments, the public attempts to consider that psychiatrists are more likely to encounter with violence and operate in a riskier setting[59,60], which were confirmed in a survey of psychiatric healthcare professionals[61]. In a study based on a sample in China, it was found that 78% of psychiatrists reported having experienced verbal abuse, compared to more than 30% who had experienced physical abuse[62]. Similar findings about psychiatrists' susceptibility to being hurt in medical injury incidents were discovered in surveys conducted in Germany[63], Ghana[64], Turkey[65], and Kuwait[66]. Psychiatrists are considered physically tainted because of the hazardous work environment.

For psychiatrists, associative stigma serves as a major source of occupational stigma[67,68]. Due to their frequent interactions with and treatment of patients with mental illness, psychiatrists may experience associative stigma that their clients may attach to them[9,69]. Patients with mental illness are a highly stigmatized group[70,71]. Their image is portrayed as negative, dangerous, and dishonest, and their social value is severely diminished[72]. To a large extent, the formation and development of stigma toward mental illness result from both religion and culture[73]. People with mental illness were thought to be possessed by evil spirits in Christianity[74] and Islam[75]. Expulsions and floggings, the confinement of mentally ill persons in jails and insane asylums, or even burning as a form of torture were all common practices in medieval Europe including Switzerland, Germany, and France[72]. Moreover, the thought of saving face is strongly ingrained in Chinese Confucian culture[76]. Concealing or avoiding the information that a family member suffers from a mental illness is typically done to preserve the family's reputation[68]. Even today, many people who suffer from mental illness and their family members still refrain from disclosing their situations to others for fear of prejudice and rejection. This ubiquitous phenomenon exists in nations where collectivist principles are valued[77,78]. The low

use of mental health services is partly caused by the stigma around mental illness[79]. Being socially tainted is, therefore, the most typical trait of psychiatrists' occupational stigma.

The possibility of being morally tainted among psychiatrists should not be overlooked. In treating people with mental illness, coercive measures such as seclusion, restraint, and forced medication are widely used[80]. Although patients perceive coercion as harmful to the treatment, healthcare professionals take it as an effective method of caring for, protecting, and treating patients[81]. Coercive measures have been the subject of heated debate in medical ethics, as well as legal scrutiny. Then, alternative options are sought and implemented by psychiatrists actively[82]. On the one hand, psychiatrists frequently consider physical and chemical restraints necessary, but on the other hand, they also recognize their potential to undermine patient rights and negatively impact the therapeutic relationship [83]. Therefore, it is understandable that psychiatrists may experience criticism, moral condemnation, and perceived intense moral pressure due to the dangers that coercive tactics may cause[84]. Now, an increasing number of researchers are advocating for improvements in the clinical practice of mental health medicine in order to reduce the use of coercive tactics[85]. In addition, electroconvulsive therapy (ECT) is frequently utilized to treat a variety of psychiatric diseases, including depression[86] and schizophrenia[87], with positive effects. However, ECT has been stigmatized and used as "proof" of psychiatrists' violence and harm to patients due to the media and the antipsychiatry movement[88]. As a result, psychiatrists also experience being morally tainted.

As illustrated above, the psychiatrists' occupational stigma is a complex idea that calls for multidimensional interpretations. Psychiatrists are seen as simultaneously being physically tainted, socially tainted, and morally tainted considering the potentially dangerous work environment, their exposure to and treatment of highly stigmatized populations, and the use of controversial and aggressive treatment methods. Occupational stigma could result in detrimental consequences for psychiatrists including isolation, discrimination, and loss of status and then made itself an indispensable factor to impede the advancement of medical and health services in mental health.

THE MEASUREMENT OF PSYCHIATRISTS' OCCUPATIONAL STIGMA

To date, no occupational stigma scales have been developed for psychiatrists. In such a pertinent quantitative investigation, this can be accomplished by adapting other occupational stigma instruments (see Table 1). There are four different categories of scales that can be used to gauge public stigma toward psychiatrists. One type is that one dimension or more of the scale's items indicates occupational stigma. Richmond *et al*[89] created the psychometrically reliable Trust in Doctors in General (T-DiG) and Trust in the Health Care Team scales (THCT) to assess public trust in medical professionals and healthcare teams. Both the T-DiG and THCT include 29 items, which are from seven dimensions that refer to stigma-based discrimination, communication skills, system trust, loyalty, confidentiality, fairness, and general trust[89]. The stigma-based discrimination dimension contains three items that doctors or people who work in health care would unfairly treat patients with a history of mental illness, HIV, or drug abuse. Although T-DiG and THCT can reflect the public occupational stigma against physicians to some extent, the richness of occupational stigma is not accessible by measuring a single dimension of the scale. Meanwhile, occupational stigma, the complex concept, must be examined from multiple perspectives. The T-DiG and THCT contain only one item, physicians' unfair treatment of patients with a history of mental illness, and can only assess specific aspects of occupational stigma.

The second is to measure patients' occupational stigma against physicians. Fan *et al*[90] developed the Patient Toward Physician Occupational Stigma Scale (PPOSS), which consists of 19 items divided into three dimensions, namely stereotype, prejudice, and discrimination. The cognitive, affective, and behavioral components of occupational stigma are measured respectively[90]. Although the PPOSS was created specifically to assess physicians' occupational stigma, there are significant differences between physicians in different departments regarding the source, type, and extent of occupational stigma[49,52,91,92]. Psychiatric patients were not chosen as the study subjects during the development of the PPOSS, and items reflecting the psychiatrists' professional characteristics were lacking. As a result, more evidence is needed to determine whether the PPOSS is suitable for assessing patients' occupational stigma toward psychiatrists.

The third is to measure the public's social distance from physicians to examine their stigmatizing attitudes. A key element of psychological distance is social distance, which measures the degree of intimacy between various groups and between people within the same cohort[93]. The Social Distance Scale (SDS) has been utilized as a measurement tool in a study to examine public stigma and public behavioral inclinations toward physicians[94]. However, the SDS was originally designated not to measure occupational stigma but to measure the public distance perception between various nations, ethnic groupings, races, or groups[95]. The concepts of social isolation and occupational stigma are not interchangeable because they have obvious distinctions. Currently, the SDS is employed in research on occupational stigma less frequently, particularly when assessing public stigma toward physicians. Only a small number of studies used the scale[96].

Table 1 Measurement tool of psychiatrists' occupational stigma

Scale title	Target	Content	Item	Dimension
[89]THCT	Public	Measure public trust in medical professionals and health care team	29	7 dimensions: Stigma-based discrimination; communication skills; system trust; loyalty; confidentiality; fairness; general trust
[90]PPOSS	Patients	Measure the cognitive, affective, and behavioral components of occupational stigma	19	3 dimensions: Stereotype (6 items); prejudice (7 items); discrimination (6 items)
[94]SDS	Public	Measure stigmatizing public perceptions of and behavioral inclinations toward the physicians	8	Single dimension
[97]Public attitudes towards psychiatrists' questionnaire	Public	Measure the public's unfavorable views and impressions of psychiatrists' professionalism, mental health, occupational authority and ethical standards	8	Single dimension
[98]OSCS	Practitioners	Measure the stigma awareness of practitioners in the service industry	6	Single dimension
[100]E16-COVID19-S	Practitioners	Measure specific aspects of physician occupational stigma	16	3 dimensions: Personalized stigma (8 items); concerns of disclosure and public attitudes (5 items); negative experiences (3 items)
[101]PSCP	Physicians	Measure perception of COVID-19-induced stigma in healthcare workers	10	2 dimensions: Environmental stigmatization; the perception of personal stigmatization
[103]Self-designed stigma questionnaire	Physicians	Measure mental health stigma	12	Single dimension
[104]DAQ	Medical students	Measure stigmatization of physicians suffering from mental disorders	3	Single dimension
[105]SOSS-D	Doctors	Measure the stigma of occupational stress and burnout among physicians	11	3 dimensions: Perceived structural stigma (5 items); perceived individual stigma (3 items); perceived other related stigma (3 items)
[106]MHPSS	Mental Health Professionals	Measure occupational stress and burnout stigma in mental health professionals	13	4 dimensions: Perceived other stigma (3 items); perceived structural stigma (4 items); personal stigma (3 items);self-stigma (3 items)
[107]PIOSS	Physicians	Measure physicians' identification with negative labels, perceptions of devaluation and discrimination, as well as the denial and disapproval of their own profession	19	3 dimensions: Label identification (5 items); status loss (8 items); career denial (6 items)
[108]FSS	Forensic	Measure internalized occupational stigma	12	2 dimensions: Dangerousness/unpredictability (7 items); responsibility/blame (5 items)
[13]Mental health professionals' questionnaire	Mental health professionals	Measure the perceived associative stigma	4	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale a)	Psychiatrists	Measure perceived stigma in terms of the perception of societal stereotypes	16	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale b)	Psychiatrists	Measure self-stigma in terms of stereotype agreement	16	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale c)	Psychiatrists	Measure perceived stigma in terms of structural discrimination	5	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale d)	Psychiatrists	Measure discrimination experiences	13	Single dimension
[110]Measuring Psychiatrist occupational stigma scale (the scale e)	Psychiatrists	Measure stigma outcomes	5	Single dimension

COVID-19: Coronavirus disease 2019; DAQ: Discriminative attitude questionnaire; FSS: Forensic Stigma Scale; OSCS: Occupational Stigma Consciousness Scale; PIOSS: Physician Internalized Occupational Stigma Scale; PPOSS: Patient Toward Physician Occupational Stigma Scale; PSCP: Perception of Stigma due to COVID-19 in Physicians; SDS: Social Distance Scale; SOSS-D: Stigma of Occupational Stress Scale for Doctors; THCT: Trust in doctors in general and Trust in the health care team scales.

Fourth, a non-standard assessment method was used to examine the public's negative perceptions of psychiatrists. Ta *et al*[97] used a self-designed Public attitudes towards psychiatrists questionnaire with eight items to assess public perceptions of psychiatrists. The questionnaire mainly measured the public's negative attitude and views of psychiatrists' professionalism, mental health, occupational authority and ethical standards[97]. Nevertheless, it is hard to state the reliability and validity of the research results because the questionnaire's reliability and validity were not assessed.

The scales that can be used to measure the self-stigma of psychiatrists could be divided into four categories. The first is the scale used to gauge psychiatrists' sensitivity to stigma. The Occupational Stigma Consciousness Scale (OSCS) is the most frequently used tool in studies on physicians' occupational stigma. The OSCS comprises six one-dimensional items that assess practitioners' perceptions of public stigmatization of their work. However, the OSCS was originally developed based on call center service workers and was primarily used to assess the stigma awareness of practitioners in the service industry[98]. According to the needs of researchers' studies, they appropriately adapted the scale for use in quantitative studies of various occupational stigma in subsequent studies[99]. It should not be ignored that psychiatrists are part of a high-prestige profession that differs significantly from dirty work regarding stigma manifestations and negative consequences.

The second is the scale for measuring specific aspects of physician occupational stigma. Based on the severe acute respiratory syndrome stigma scale, Mostafa *et al*[100] developed the new coronavirus disease 2019 (COVID-19) Stigma Scale (E16-COVID19-S)[100]. Similar to this, Oktar *et al*[101] developed the Perception of Stigma due to COVID-19 in Physicians (PSCP) with 10 items, including two dimensions that are environmental stigma and individual stigma perception[101]. These two scales measure specific components of physicians' occupational stigma, but fail to reflect its full spectrum of connotations.

The stigmatization of occupational stress and burnout among physicians has been the research focus in this field. For instance, Riley *et al*[102] discovered that physicians experience high stigma in mental health, work stress and burnout, manifested as inability to admit vulnerability and insistence on working, even if unwell[102]. A study by Wijeratne *et al*[103] on physicians' mental health stigma found that they tend to conceal their mental health conditions from colleagues and are less likely to seek help because there is a belief that physicians suffering from depression or anxiety disorders are perceived as untrustworthy[103]. This study applied a self-designed 12-item stigma questionnaire as a survey tool, which was not strictly tested for reliability nor validity, but only reported internal consistency coefficient values. Zarzycki *et al*[104] adopted a self-designed Discriminative Attitude Questionnaire (DAQ) to examine medical students' stigmatization of physicians with mental disorders[104]. The DAQ includes only three non-standardized items and is only applicable for assessing stigma regarding mental disorders. Furthermore, Clough *et al*[105] developed the 11-item Stigma of Occupational Stress Scale for Doctors (SOSS-D). There are three dimensions extracted in the SOSS-D including perceived structural stigma, perceived individual stigma, and perceived other related stigma[105]. To measure occupational stress and burnout stigma in mental health professionals, Clough *et al*[106] created the Mental Health Professional Stigma Scale (MHPSS)[106]. There are 17 items total in the MHPSS, which are broken down into four dimensions: Perceived other stigma, perceived structural stigma, personal stigma, and self-stigma. Stigmatizing attitudes, stress and burnout among psychiatrists can pose serious threats to their professional development. However, scales for measuring the stigma of occupational stress and burnout specifically among psychiatrists are lacking and should be developed in future research.

The third part include scales for assessing physicians' internalized occupational stigma. Fan *et al*[107] created a 19-item Physician Internalized Occupational Stigma Scale (PIOSS) divided into three dimensions including label identification, status loss, and career denial. The PIOSS scale is primarily used to evaluate physicians' identification with negative labels, perceptions of devaluation and discrimination, and denial and disapproval of their profession[107]. Besides, Healey *et al*[108] developed the Forensic Stigma Scale (FSS) with 12 items falling into two dimensions that refer to danger/unpredictability and blame/responsibility[108]. Although PIOSS and FSS have strong validity and reliability, the study subject did not include psychiatrists.

Fourth, there is a non-standard tool for assessing the perception of stigma among psychiatrists. A self-designed mental health professional's questionnaire was used in the study by Verhaeghe *et al*[109] Four items comprise the questionnaire, which mainly measures the perceived associative stigma among psychiatrists and other mental health professionals. However, Cronbach's alpha coefficient for the questionnaire was just 0.51 since it had not undergone a rigorous reliability test[109].

Fifth, there is a scale specifically designed to measure the occupational stigma of psychiatrists. The World Psychiatric Association (WPA) has developed specific action plans to reduce the stigma toward psychiatry and psychiatrists. One of the essential tasks is to develop standardized questionnaires[110]. The basic version comprises five scales: (1) Perceived stigma in terms of the perception of societal stereotypes; (2) self-stigma in terms of stereotype agreement; (3) perceived stigma in terms of structural discrimination; (4) discrimination experiences; and (5) stigma outcomes. The scales (1) and (2) consist of 16 items measuring the professionals' competence, professional conduct, and personality, as well as the stigma of psychiatry as a medical specialty and its treatment methods. Scale (3) and scale (5), consisting of five items, assesses the social aspects of stigma and the negative consequences of stigma. Scale (4)

consists of 13 items, assessing experiences made in contact with doctors from other disciplines and experiences made in personal life. The scale developed by the WPA is a valid tool for assessing the internalization of occupational stigma among psychiatrists.

THE INTERVENTION OF PSYCHIATRISTS' OCCUPATIONAL STIGMA

The study of stigma intervention strategies has been the main research subject in the stigma field. To effectively intervene with various demographics and stigma, the approaches used can be cross-referenced[111,112]. In a systematic evaluation of stigma intervention strategies, which included research findings from various countries (low-, middle-, and high-income), stigmatized populations (such as those with AIDS, mental health disorders, and leprosy), intervention targets (such as medical personnel, family members, and community members), and intervention strategies (such as contact, education, and training), the analysis discovered some similarities in the strategies, measures, and intervention outcomes achieved when intervening with different types of stigma[113]. A review of stigma intervention strategies can serve as a theoretical foundation for psychiatrists' occupational stigma intervention practice. Stigma intervention strategies can be roughly classified into six categories.

First, the protest approach is a strategy for the stigmatized community to voice their opinions and express their disapproval through public declarations, media exposure, and stigma-related commercials to minimize stigma[114]. However, protest tactics risk escalating stigma, leading to public conflict and rebellion[115]. Therefore, they are used relatively infrequently. Furthermore, compared to more conventional rallies and demonstrations, the usage of social media platforms on the internet is growing. For instance, rebuttals to stigmatizing attitudes about mental illness are shared on Twitter during Mental Health Awareness Week, an annual effort in May[116]. Similarly, Depression Awareness Week is coordinated on Twitter with the primary objective of lowering the stigma attached to mental illness [117].

Second, educational strategies are applied to alter erroneous beliefs and reduce stigma by delivering accurate information to the intervention target[118]. A few commonly employed techniques are class lectures, anti-stigma training, special lectures, workshops, role plays, case studies, watching instructional videos, reading professional publications, and creating self-reflection reports (see Table 2). In the pertinent literature, more attention is paid to the stigmatization of medical professionals and the general public toward people with mental illnesses. In contrast, relatively few research studies have been conducted on psychiatrists' occupational stigma. Educational strategies effectively change healthcare professionals' attitudes toward patients with mental illnesses and increase contact willingness and frequency[119-122]. Besides that, it is conducive to reducing self-stigma in patients with mental illnesses through education[123]. Moreover, interventions can be implemented in stand-alone educational formats, such as workshops[124] and educational videos[125], or in a combination of formats to achieve more significant results. For example, in Education Not Discrimination[126] and Mental Health First Aid[127], a combination of presentations, videos, action plan ideas, case discussions, and role plays is used.

Third, the contact strategy aims to strengthen relationships with stigmatized people to alleviate adverse stereotypes. In stigma interventions, the contact strategy has been applied most frequently and has produced promising benefits[128]. It is possible to boost intergroup connections and minimize prejudice by increasing the frequency of public contact with stigmatized individuals, especially high-quality contact[129]. According to Corrigan *et al*[130], contact approaches are approximately three times more effective than educational strategies with more prominent and persistent impact[130]. Even short-term exposure has the potential to improve attitudes and understanding about stigma[131] and lower stigma levels[132]. The question of how to accomplish the desired intervention outcomes and guarantee the effectiveness of the contact method has always been the focus of scholars[131]. Corrigan *et al*[133] proposed that the most critical factors influencing the effectiveness of interventions are design, target, staff, message, evaluation and follow-up in five areas[133]. Specifically, the intervention can be delivered face-to-face, with a person with extensive life experience serving as a speaker, designing a program that matches the target audience's characteristics and delivering the intervention through storytelling. After the intervention's completion, evaluation and follow-up of the intervention effects are also required[134].

In terms of forms of intervention, direct and indirect contact are included[135].Direct contact as a promising anti-stigma strategy can improve communication and cooperation between patients with mental illnesses and other patients, as well as between patients and family members and the general public[136]. By increasing contact between health science students and people with mental illnesses in the Co-Production with Dialogue Program for Reducing Stigma, it is possible to significantly reduce public stigma and improve mutual understanding between patients and students[137]. Psychoeducational materials, face-to-face workshops, and interventions based on cognitive behavioral therapy were generally well received in the workplace-based multi-country intervention tackling depression, anxiety, and mental illness-related stigma study[138]. In the "Honest, Open, Proud" project, self-exposure and community-based participatory research were used to reduce self-stigma among individuals with

Table 2 Intervention of education

Strategy	Target	Content	Objective
[119]Education training	Family caregivers of patients with schizophrenia	Teaching related knowledge and skills (90 min/8 sessions)	Reduce stigma toward patients with schizophrenia
[120]Anti-stigma training	Care assistant workers	Financial assistance policy of care assistant workers + mental health knowledge (2 h) + stigma related to mental illness (1 h)	Reduce stigma toward patients with mental illness
[121]Anti-stigma training	Community mental health staff	Two parts: Knowledge introduction + stigma related to mental illness (1 d)	Increase mental health knowledge; Reduce stigma toward patients with mental illness and social distance
[122]Anti-stigma training	Probation officers	Six modules in PPT about overview of severe and persistent mental illnesses; information about key diagnoses and the medications; services associated with those diagnoses	Increase mental health knowledge; Reduce stigma toward mental illness and behavior tendency
[123]NECT	Persons with severe mental illness	20 sessions (1 h): (1) Introduction (1 wk); (2) Psychoeducation (3 wk); (3) Cognitive restructuring (8 wk); and (4) Narrative enhancement (8 wk)	Reduce stigma toward mental illness
[124]Educational workshop	High School Students	Classroom-based workshop: (1) Introduction: Mental illness and public stigma; (2) Education; and (3) Treatment of mental illness and available community resources (1 h)	Reduce stigma toward mental illness
[125]Educational videos	High school students and college students	Educational film (10 min): (1) BMM about mental illness; or (2) RCM advocated by experts	Reduce more stigma in BMM than RCM
[126]END	Medical students	Short lecture; testimonies about the experiences and stigma; role-plays	Increase mental health knowledge; Reduce stigma toward mental illness and behavior tendency
[127]Mental health first aid training	Pharmacy and non-pharmacy students	Identify, understand, and respond to signs of mental illnesses and substance use disorders (8 h); Methods: Videos, role play sessions, action plan creation, discussion, and other interactive activities	Reduce stigma toward mental illness

BMM: Biomedical messages; END: Education not discrimination project; NECT: Narrative enhancement cognitive therapy; PPT: Power point; RCM: Recommended messages.

mental illness[139].

The typical indirect contact method is video contact. Researchers prefer video contact because of its low cost, broad audience reach, reusability, low resource possession, and ease of dissemination[130]. Short video interventions are an essential and effective intervention in studies of depression stigma and help-seeking attitude stigma[140], mental health-related stigma[141], and mental illness stigma[142].

Fourth, comprehensive strategies combine two or all three of the protest, education, and contact strategies. Education and contact strategies are most frequently employed (see Table 3). For instance, Tan *et al*[143] discovered that increasing interaction (direct contact) and attending lectures (education) improved people's attitudes and levels of acceptance toward those who suffer from depression[143]. Furthermore, a three-stage intervention paradigm was subsequently developed by Ahuja *et al*[144]. Specifically, participants in the intervention were required to watch a dance drama to learn about common misconceptions and correct perceptions of mental illness. Then, individuals were asked to listen to an informational lecture and directly communicate with people suffering from mental illness. Hawke *et al*[145] used an indirect intervention strategy, showing the recorded stage play to healthcare providers, college students, people with bipolar disorder and their friends and family members, and the general public. The findings revealed that education and exposure *via* video approach similarly reduced the stigma of bipolar disorder among intervention subjects and had sound delayed effects[145].

Some studies have attempted to integrate anti-stigma education into school curricula. Ma *et al*[146], for example, designed a teaching component covering knowledge, experience, and action, as well as education strategies, direct contact, and indirect contact, to reduce the stigma of mental illness among medical students[146]. Case discussions and systematic curriculum instruction[147,148] can be used to achieve intervention goals[149]. Both educational and direct contact strategies, as well as educational and indirect contact strategies, have demonstrated practical intervention effects[150-168]. However, in a study of an adolescent population, educational strategies alone were superior to combined education and contact strategies in reducing mental illness stigma[165]. The researchers suggest that the young age of the intervention subjects may have contributed to this result and that contact strategies should be used with caution when intervening with adolescents. As a result, more evidence is needed to determine whether the combined strategy is superior to the single intervention strategy in various age groups.

Fifth, systematic intervention strategies emphasize the importance of considering the interplay of factors at different levels when intervening with stigma and integrating different types of intervention

Table 3 Intervention of comprehensive strategies

Strategy	Type	Content	Target	Objective
[143]Lecture	Education + direct contact	Video + personal experience + questions and answers (50 min)	Undergraduate	Increase knowledge of depression and help-seeking willingness
[144]Three-stage intervention paradigm	Education + direct contact + indirect contact	Dance-drama + lectures + direct contact (2 h)	Undergraduate	Increase understanding and tolerance toward patients with mental illness; Decrease negative review, negative labels and social distance toward patients with mental illness
[145]Filmed theatrical intervention based on a personal narrative	Education + indirect contact	Filmed version of a one-woman stage play performed by a recognized educator and speaker on the lived experience of mental illness and recovery (50-min)	Health-care service providers, university students in a health-care-related course, people with BD and their friends and family members and the general public	Decrease stigma toward people with BD among health-care service provider (significant/sustainable); others (more limited)
[146]Course	Education + direct contact + indirect contact	Lecture + watch videos/movie + in-class discussion + direct contact + roleplay + action project (18 wk)	Occupational therapy students	Decrease stigma toward mental illness and social distance
[147]Course	Education + direct contact + indirect contact	Teaching (42 h) + movie (3/4 h) + contact + presentations (2 h) + clinical correlations (6 h)	Medical students	Increase student confidence; Decrease stigma toward mental illness
[148]Course	Education + direct contact + indirect contact	Face-to-face (45 min) + video-based contact (40 min) + educational lecture (90-min)	Medical students	Decrease stigma toward mental illness
[149]Case discussion	Education + direct contact + indirect contact	Document patient strengths and treatment recommendations; Group presentation discussion (10 wk)	Primary care providers	Increase willingness to help and hope for recovery; Decrease negative stereotypes
[150]Course	Education + direct contact	Personal experience + questions and answers (69-90 min)	Pharmacy students	Decrease stigma toward mental illness
[151]Workshop	Education + direct contact	Workshop (4 d): Knowledge teaching + personal experience + questions and answers	Public Health Services administrators	Decrease stigma toward patients with mental illness
[152]Workshop	Education + direct contact	Workshop (1 h): Knowledge teaching + personal experience	Social work students	Decrease stigma toward mental illness
[153]Course	Education + direct contact	Panel discussion (2 h) + visit rehabilitation center + Small group discussion (20 min)	Medical students	Decrease stigma toward patients with mental illness and psychiatry
[154]Curriculum	Education + direct contact	Courses + clinical practice + stigma views and policy (14 d)	Community mental health staff	Increase related knowledge; Decrease stigma
[155]Education program	Education + direct contact	Enhancing contact model: Psychoeducational training (4 wk) + single and group family contact (8 wk)	Family caregivers of persons with schizophrenia	Decrease stigma toward mental illness
[156]Education program	Education + direct contact	Lectures (2 h) + contact with people with lived experience of mental illness (1 h)	Community health and care staff	Decrease stigma toward mental illness
[157]Course	Education + indirect contact	Teaching + videos (3 h)	Psychology students	Improve attitude toward schizophrenia
[158]Virtual program	Education + indirect contact	Three consecutive interventions (14 h/2 d): 2 sessions (2.5 h) + e-contact (3.5 h) + project-based learning (5.5 h)	University students	Decrease stigma toward mental disorders
[159]Educational video	Education + indirect contact	Social contact film with general mental health education (30 min/2 mo intervals in 1 year)	University students	Decrease mental illness-related stigma
[160]Course	Education + indirect contact	Interactive workshop-style sessions (3.5 h/15 wk)	Primary care physicians	Increase skill and confidence; Decrease stigma toward mental illness
[161]Educational	Education +	Video-based contact intervention	Primary care nurses	Improve attitude toward patients with

Video	indirect contact	(VBCI): Elements of psychoeducation and interviews (5 min)		mental illness in short term
[163]Educational video	Education + indirect contact	YouTube videos (5-10 min)	Muslin adults aged 18 and over	Decrease stigma toward mental illness
[164]Lecture	Education + direct contact	Personal experience + Interaction	High school students	Decrease stigma toward mental illness
[165]Education program	Education + direct contact	Educational program (1 d)	Adolescents	Education decreases stigma toward mental illness; Direct contact fails
[166]Course	Education + direct contact	Education with PBL: Problem-based learning model + direct contact	Nursing students	Improve positive attitude toward mental illness
[167]Online focus group	Education + direct contact + indirect contact	Education + relationship strategies + media contact	Senior undergraduate nursing students	Minimize the negative impact on the people they take care of
[168]Sessions	Education + direct contact	Five sessions (3 d)	Caregivers of mental health service users	Improve family relations and understanding of mental illness

BD: Bipolar disorder.

strategies into a unified framework[162]. According to Heijnders and Van Der Meij[169], the effects obtained by employing a single level of intervention strategy or intervening with a single target group are frequently insufficient and necessitate the integration of multiple factors[169]. As a result, Cook *et al*[170] developed a three-level ecosystem model that divides stigma intervention strategies into individual, interpersonal, and structural levels, arguing that interventions at any level can affect the effectiveness of interventions at other levels[170]. Individual-level interventions concentrate on enhancing coping mechanisms used by stigmatized individuals or altering the attitudes and conduct of stigma abusers. By enhancing engagement and contact between the group of stigma abusers and the group being stigmatized, interpersonal interventions aim to reduce intergroup barriers and foster greater mutual understanding. Through the creation of pertinent laws and regulations to lessen prejudice and discrimination, intervention at the structural level is primarily seen from the perspective of the socio-political environment.

Additionally, Heijnders and Van Der Meij[169] suggested a five-level stigma intervention program (individual level, interpersonal level, social level, organizational and institutional level, and governmental level)[169]. In particular, professional counselling and therapy can be used at the individual level to help the stigmatized population cope with stigma; interventions at the interpersonal level concentrate on improving how the stigmatized population interacts with the elements of their environment in order to gain care and support; and interventions at the social level focus on changing public attitudes through education, advocacy, or contact strategies. At the organizational and institutional levels, specialized training or the development of internal systems can be adopted to reduce stigma in a group, organization, or institution; at the government level, interventions focus on the establishment of relevant laws and policies, as well as the use of coercive measures, to reduce stigmatized speech and behavior.

Sixth, increasing researchers have attempted to incorporate psychotherapeutic approaches and techniques into stigma interventions and have achieved promising results (see Table 4). Hong *et al*[171] used mindfulness training to intervene with self-stigma in depressed patients and got excellent and long-lasting results[171]. It was found by Clinton *et al*[172] that Positive Empathy Intervention (imagining positive contact with the stigmatized person and establishing a positive emotional connection) was superior to traditional contact methods in terms of stigma reduction[172]. Cognitive-behavioral Intervention and Wise Intervention have been shown to increase perceived social support and reduce self-stigma in individuals[173,174]. Furthermore, Visual Information Image Interventions [175] and Work Integration[176] assist individuals in gaining correct knowledge, changing perceptions, and enhancing social inclusion, thereby reducing stigma.

Art Therapy is currently widely applied in the work practice of mental health education in schools. When intervening with the stigma of mental illness in adolescents, art therapy methods such as film, drama, and role-playing can be adopted[177,178]. Picture storytelling or fiction writing can enable the individual's indirect contact with an AIDS patient[179]. The Petkari's study[180] discovered that watching a series of movies about mental illness (over 10 wk) accelerated college students' agency, compassion, and proximity toward patients[180]. Acceptance and Commitment Therapy (ACT), based on relational framework theory, has been dubbed the "Third Wave" of behavioral therapy[181]. In interventions for weight stigma[182], substance use disorder stigma[183], and homosexuality stigma [181], ACT has shown significant positive effects. Furthermore, Narrative Therapy[184], Written

Table 4 Other intervention strategies

Strategy	Objective
[171]Positive thinking training	Intervene with self-stigma in depressed patients
[172]Positive empathy intervention	Establish a positive emotional connection with stigmatized person to reduce stigma
[173]Cognitive-behavioral intervention	Reduce self-stigma associated with mental illness
[174]Wise intervention	Increase perceived social support; Reduce personal discrimination
[175]Visual information image intervention	Increase sense of support and engagement; Reduce stigma
[176]Work integration	Reduce perceived stigma of workers with serious mental illness
[177-180]Art therapy	Reduce mental illness stigma of adolescents
ACT	Reduce weight stigma[182], substance use disorder stigma[183], and homosexuality stigma[181]
[184]Narrative Therapy	Reduce the level of stigma for patients with permanent enterostomies
[185]Written expression-based emotional intervention	Reduce negative emotion
[186]Sand tray therapy	Improve the development of self-esteem in sexually abused adolescents
[187]CBGT	Reduce the level of stigma in the population of people living with HIV
[188]Intergenerational choir	Reduce the stigma of Alzheimer's patients and increasing positive attitudes
[189]FSM	Reduce stigma and promote mental health help-seeking behavior

ACT: Acceptance and commitment therapy; CBGT: Compassion-based group therapy; FSM: Fresh start mindset framing.

Expression-based Emotional Intervention[185], Sand Tray Therapy[186], Compassion-Based Group Therapy[187], Intergenerational Choir[188], and Fresh Start Mindset Framing[189] can be used as stigma interventions.

To summarize, in the intervention of psychiatrists' occupational stigma, protest, education, contact, integrated and systematic intervention strategies, and multiple approaches such as positive thinking training, cognitive behavioral therapy, ACT, and art therapy are available to be adopted. In order to achieve optimal results, the appropriate intervention method must be chosen based on the characteristics of the intervention target. It should be noted that while the above intervention strategies have been applied to various types of stigma interventions with positive results, more evidence is needed to support whether the strategies mentioned above are applicable to psychiatrists' occupational stigma interventions and how they can be implemented to achieve significant intervention effects.

DISCUSSION

In summary, previous studies have yielded results regarding the concept, measurement, and intervention of psychiatrists' occupational stigma. Nevertheless, there is room for improvement in this field. This review aimed to elaborate on the thinking and practices of related issues. Therefore, future research should consider improving on the four aspects outlined below.

First, clarify and refine the concept of psychiatrists' occupational stigma. Although various scholars have defined the concept of occupational stigma, related research has focused more on dirty work. Indeed, there is a paucity of research specifically on psychiatrists' occupational stigma. Based on Ashforth and Kreiner's research[43], this paper elaborates on the sources and dimensions of psychiatrists' occupational stigma, namely physically, socially, and morally. This theoretical framework allows for the development of relevant quantitative research and intervention studies. Although Ashforth and Kreiner's concept[43] of occupational stigma has gained widespread acceptance, it is not formally classified other than according to the work content of an occupation. As such, it does not reflect the cognitive, emotional or behavioral components of occupational stigma. In addition, the understanding of occupational stigma is not consistent across disciplines. Future research should combine theories from other disciplines (including individual cognitive models, social identity theory, self-verification perspectives, and other conceptual models) to further explore and extend the conceptual connotations of psychiatrists' occupational stigma. Furthermore, the theoretical framework of occupational stigma should be combined with statistical analysis to determine the multiple dimensions of psychiatrists' occupational stigma. This study provides such a theoretical basis for future measurement and intervention studies.

Second, develop specific tools to measure psychiatrists' occupational stigma. Lately, as public awareness of the harm of occupational stigma has increased, relevant measurement tools have been refined. However, some existing instruments are not sufficiently reliable nor valid, and tools specifically designed to assess psychiatrists' occupational stigma are lacking. As no consensus exists on the conceptual and operationalization scope of occupational stigma, there is inconsistency in developing relevant dimensional and measurement scales. Furthermore, most tools lack rigorous cross-cultural consistency. Future research should consider the following: (1) Define the dimensional scale and classification of psychiatrists' occupational stigma based on a multidisciplinary synthesis; (2) Develop special assessment tools for different stigma types (public stigma and self-stigma) and cohorts (psychiatrists, psychiatric students, mental illness patients, patients' families, and the public); (3) Expand the sample scope across different races, countries and age ranges to determine the impact of cross-cultural backgrounds and generational effects on the results; and (4) Based on traditional self-reporting questionnaires, adopt more indirect survey methods such as virtual reality technology, videos, or games allowing for measurement methods with higher ecological validity and aligned to life situations that yield a realistic and contextualized understanding.

Third, improve intervention strategies for psychiatrists' occupational stigma. Intervention strategies specifically applicable to psychiatrists' occupational stigma are currently lacking. Initially, when intervening for psychiatrists' occupational stigma, other types of stigma intervention strategies may be considered. However, undoubtedly these could lead to biases in the effectiveness of the intervention. Therefore, future studies should test whether existing intervention strategies are suitable for psychiatrists. Follow-up horizontal comparison and longitudinal studies can be conducted on the effects of the three common intervention strategies (protest, education, and contact), as well as integrated, systematic, or other strategies, seeking to find the most appropriate traditional intervention strategies and setting for psychiatrists. It is necessary to acknowledge that stigma may exacerbate or impede such processes as psychological[190,191] and behavioral responses[192,193] or social relationships, intensifying stress and burnout that could result in mental health disorders. Some studies have demonstrated that educational interventions which provide in-depth information about the negative effects of stigma on mental health professionals can be effective in decreasing stigma, especially for general healthcare professionals with little or no formal mental health training. Alternatively, future research should develop unique, simple, and effective intervention strategies tailored to the characteristics of psychiatrists. Combining intervention studies with experimental studies could identify simple and accessible ways to reduce occupational public stigma directed toward, and self-stigma experienced by, psychiatrists. Importantly also consider that the effects of a particular intervention may not be uniform among psychiatrists from different countries, cultural backgrounds, or years of practice. Thus, when formulating intervention strategies, full consideration should be given to differences in intervention targets.

Fourth, identify cross-cultural consistency or differences in psychiatrists' occupational stigma. Self-evidently, psychiatrists' occupational stigma can vary culturally. Future research should explore the consistency or differences in occupational stigma concepts, measurements, and interventions among psychiatrists in cross-cultural settings. For example, in Chinese culture, traditional ideas conveyed across millennia, such as Confucianism, Taoism, Buddhism, and folklore, have influenced Chinese thinking and behavior towards self-regulation; this combined with strong family values and a face-saving culture, deems mental illness as both a personal sin and a family shame[194]. Other regions may have different stigma levels toward mental illness[195], so cultural traditions may influence the inception of psychiatrists' occupational stigma. Is it possible that perceptions of psychiatrists' occupational stigma differ across cultures? Dose this influence the measurement and treatment of psychiatrists' occupational stigma? Such interrogations have yet to be confirmed through in-depth research.

LIMITATIONS

It should be acknowledged that there were certain deficiencies in the process of screening and synthesizing many studies in this literature review. First, the selection criterion, which only considered English and French literature, was limiting. Therefore, it is possible that relevant studies that satisfied other inclusion criteria were excluded. Thus, overall integrity is somewhat lacking. Second, the literature search was carried out by both professors and students. Irrelevant studies, duplicates, or those arising from incorrect search results were excluded. However, given the excessive literature search results, no secondary duplication test was undertaken. Therefore, it is impossible to determine whether excluded studies should have been included, indicating a lack of rigor. Finally, this review was based on the authors' analyses and synthesis of the literature; although the study seeks to remain objective, it contains some subjectivity.

CONCLUSION

By surveying the existing literature, this literature review has proposed a theoretical reference of the concept, measurement, and intervention methods for psychiatrists' occupational stigma. Psychiatrists' occupational stigma is a complex concept that should be interpreted in multiple dimensions. Psychiatrists are associated with three types of stigma (physical, social, and moral taint) because of the dangers of their work environment, their exposure to and treatment of high-stigma groups, or their use of controversial or aggressive treatments. Currently, there is no occupational stigma scale applicable specifically to psychiatrists. Relevant quantitative research could achieve this by adapting other occupational stigma scales. Table 1 summarizes eight possible categories of occupational stigma measurement tools for psychiatrists, including four types for public stigma and another four for self-stigma. Currently, there are few studies on occupational stigma interventions for psychiatrists. Therefore, a theoretical reference for identifying relevant intervention practices for psychiatrists' occupational stigma is required. This study has classified such stigma intervention strategies into six categories: Protest, education (Table 2), contact, comprehensive strategies (Table 3), systemic strategies, and means of incorporating psychotherapeutic approaches (Table 4).

Given that research on psychiatrists' occupational stigma has received insufficient attention and discussion in the academic community, this study provided a theoretical basis and support for future practical research. The theoretical significance of this review lies in that it refines the concept and structure of psychiatrists' occupational stigma, expands the general research field of occupational stigma, and encourages the mutual discussion of multi-disciplinary occupational stigma theories. This study further outlines relevant empirical research for the development of specialized measurement tools and creative implementations of effective interventions to reduce psychiatrists' occupational stigma, thereby promoting the healthy development of psychiatry and physician-patient relationships.

FOOTNOTES

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MINIREVIEWS

Epigenetics in psychiatry: Beyond DNA methylation

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Abstract

The global burden of psychopathologies appears to be underestimated, since the global psychiatric disorder burden is exceeding other medical burdens. To be able to address this problem more effectively, we need to better understand the etiology of psychiatric disorders. One of the hallmarks of psychiatric disorders appears to be epigenetic dysregulation. While some epigenetic modifications (such as DNA methylation) are well known and studied, the roles of others have been investigated much less. DNA hydroxymethylation is a rarely studied epigenetic modification, which as well as being an intermediate stage in the DNA demethylation cycle is also an independent steady cell state involved in neurodevelopment and plasticity. In contrast to DNA methylation, DNA hydroxymethylation appears to be related to an increase in gene expression and subsequent protein expression. Although no particular gene or genetic locus can be at this point linked to changes in DNA hydroxymethylation in psychiatric disorders, the epigenetic marks present good potential for biomarker identification because the epigenetic landscape is a result of the interplay between genes and environment, which both influence the development of psychiatric disorders, and because hydoxymethylation changes are particularly enriched in the brain and in synapse-related genes.

Key Words: Mood disorders; Suicide; Schizophrenia; Bipolar disorder; Hydroxymethylation; 5-hydroxymethycytosine; Gene expression

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Core Tip: DNA hydroxymethylation is one of the least investigated epigenetic mechanisms but based on currently available results it is abundant in the brain, thus potentially influencing the development of psychiatric disorders through modulation of gene expression. Currently no particular genetic locus or gene can be linked to hydroxymethylation in psychiatric disorders. However, the dynamics in gene expression of the ten-eleven translocation enzymes that catalyze hydroxymethylation have been demonstrated, and changes in hydroxymethylation levels when comparing healthy subjects with psychiatric disorders can be determined using genome-wide and candidate gene approaches.

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INTRODUCTION

The global burden of psychiatric disorders

Psychiatric disorders comprise different types of mental disorder, including anxiety disorder, major depressive disorder (MDD), bipolar disorder (BP), post-traumatic stress disorder, schizophrenia (SZ), eating disorders, neurodevelopmental disorders, disruptive behavior, and dissocial disorders. All disorders have in common a clinically significant disturbance in an individual's cognition, emotional regulation, or behavior and are normally associated with distress or impairment in important areas of functioning. In 2019, there were 970 million people around the world living with a psychiatric disorder. More than half of those people struggle with anxiety disorder (301 million) or depression (280 million), both of which are also common in children and adolescents. BP was experienced by 40 million people, and SZ by approximately 24 million people[1]. Obsessive-compulsive disorder (OCD) affects 1%-3% of the worldwide population[2]. Suicide is strongly connected with psychiatric disorders (in particular, depression and BP). However, many suicides happen impulsively in moments of crisis, such as breakdown in the ability to deal with life stressors, such as financial or relationship problems, chronic pain, or illness. More than 700000 people die due to suicide and there are many more people attempting it[3]. 13% of the global population is living with a psychiatric disorder which has a substantial effect on all areas of life, such as school or work performance, relationships with family and friends, and the ability to participate in the community[4]. Besides social impact, there is also an economic burden that costs the global economy US$ 1 trillion each year[5].

Biomarkers and psychiatric disorders

A biomarker is a measurable indicator of some biological state or condition. Diagnostic biomarkers serve for narrowing down diagnoses specific to an individual patient[6]. In the field of psychiatry, diagnoses are made based on psychiatric examination using the Diagnostic and Statistical Manual or Mental Disorders or International Classification of Diseases[7,8]. As clinical presentations of the same psychiatric disorders are heterogeneous, identifying biomarkers is essential step to facilitate diagnosis through markers that allow stratification of groups within the syndrome, early detection of the disease, prescribing the right medications, and improving treatment outcome[6]. Several factors, including genetic, neurobiological, cultural, and life experiences and their interplay contribute to psychiatric disorders. Heritability plays one part in understanding pathogenesis. For example, for the development of SZ and BP there is an approximately 80% contribution of heritability, while this drops to only around 40% for depression and suicidality[9]. Scientists have tried to understand the association of genetic polymorphisms on bigger cohorts by way of genome-wide association studies (GWAS), but there still remain many unanswered questions. This indicates that environmental factors also need to be taken into account[10]. Epigenetic mechanisms such as DNA methylation and hydroxymethylation, histone tail modifications and non-coding RNAs, respond to environmental factors and cause changes in gene expression or translation without changing DNA sequence[9]. The final biological outcome results from the interplay between different epigenetic mechanisms. In recent years hydroxymethylation has received increasing attention in the "neuroepigenome"[10]. There is particular interest in hydroxymethylation because it is highly enriched in brain and synapse-related genes, and exhibits dynamic regulation during development[11].

EPIGENETICS OF PSYCHIATRIC DISORDERS

DNA methylation

Mental disorders are influenced by many biological and external factors that can be linked together by epigenetics[9,12]. The term epigenetics describes innate (hereditary) or lifetime-acquired changes in gene expression that do not originate from differences in DNA sequence[13]. Epigenetics can thus help us understand the delicate interplay of environmental and genetic influences within the cell. One of the commonly studied mechanisms of epigenetic regulation is DNA methylation and the changes in its pattern. During the DNA methylation process a single methyl group is attached to the 5′ C site of the cytosine, making the cytosine either methylated or, when removed, unmethylated. DNA methylation can have a significant effect on the regulation of gene expression[14]. While DNA methylation is still the best researched and understood epigenetic modification, other types (such as noncoding RNAs) are getting more recognition[15,16].

DNA hydroxymethylation

DNA methylation was long thought of as a binary state; whether the switch was turned on (resulting in a methylated cytosine) or off (resulting in an unmethylated cytosine). However more recently it has been discovered that methylation can have stable intermediate stages, which can happen during the process of demethylation. Active demethylation is catalyzed by enzymes of the ten-eleven translocation (TET) family and the enzyme thymine-DNA glycosylase mediated base excision. TET family proteins (the enzymes TET1, TET2 and TET3) are 2-oxoglutarate and Fe(II)-dependent dioxygenases, which catalyze 5-methylcytosine (5mC) conversion to 5-hydroxymethycytosine (5hmC) (illustrated in Figure 1). DNA hydroxymethylation was first described in 1972 but it was only in 2009 that 5hmC was identified as an oxidation metabolite of DNA methylation[17,18]. 5hmCs are often localized in gene bodies and untranslated regions. Compared to methylation, levels of 5hmC are lower (roughly 10% of methylation levels), but a high abundance of 5hmC is observed in the central nervous system. Animal studies demonstrate that DNA hydroxymethylation appears to be important during neurodevelopment as levels of 5hmC in mice embryos increase in the absence of demethylation, making it a stable cell state. This is confirmed by many animal studies[19]. 5hmC can be recognized by specific binding proteins, and can be maintained through cell division[20]. While its exact role in adult brain is not known, it appears that DNA hydroxymethylation can affect neuroplasticity and neurotransmission. 5hmC as such serves a dual role, not only as an intermediate of active demethylation but also as an important mark of epigenetic regulation. As with DNA methylation, numerous environmental factors such as medication, stress and pollutants can affect levels of 5hmC[19].

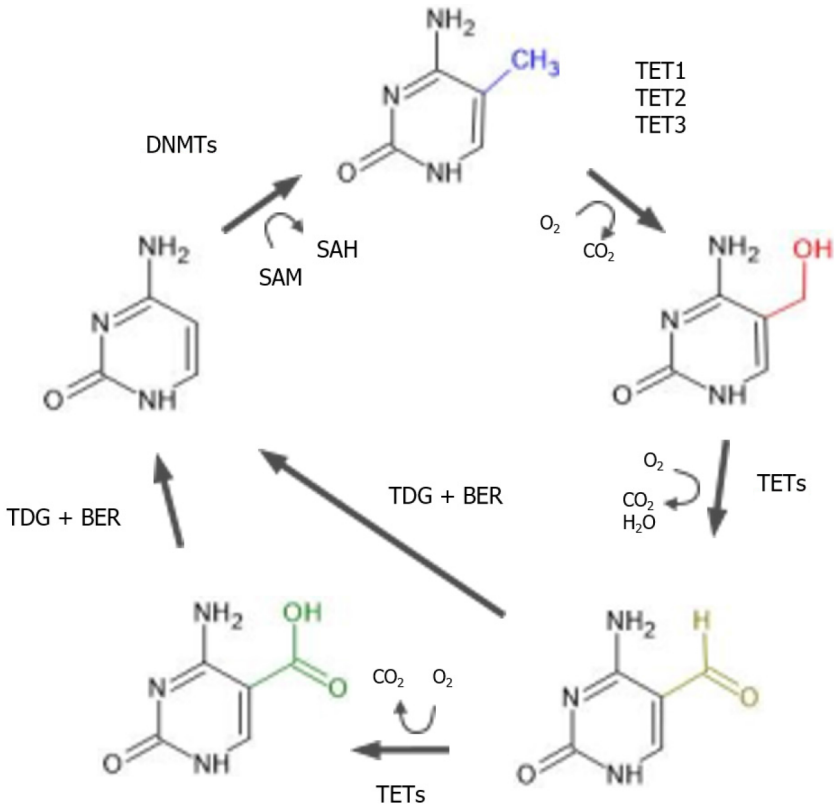
Like DNA methylation, DNA hydroxymethylation also affects gene expression, but the manner and direction (upregulation or downregulation of gene expression) are not as well characterized as for DNA methylation. Nevertheless, research indicates that DNA hydroxymethylation of the gene body leads to increased gene expression. Enrichment of DNA hydroxymethylation is also often observed at 5′ splicing sites, enhancers and CpG island borders[21].

METHODS FOR DNA HYDROXYMETHYLATION DETECTION

Several methods are available for the analysis of DNA hydroxymethylation, following in the footsteps of DNA methylation methods. For DNA methylation, bisulfite conversion of DNA is the gold standard. During the conversion, unmethylated cytosines are deaminated, allowing methylated cytosines to be identified. However, the classical bisulfite conversion approach does not work for DNA hydroxymethylation because it is not possible to distinguish between methylated and hydroxymethylated cytosines[22]. Since the ratio of methylation to hydroxymethylation is approximately 9 to 1 in favor of methylation other approaches are needed to measure hydroxymethylation[23]. When the number of target genes is small, the candidate gene approach is most appropriate. When the number of target genes increases, a genome-wide approach is usually better in terms of finances, time, and information. Therefore, the selection of the appropriate method for DNA hydroxymethylation analysis should be based on the broader experimental design. Since genome-wide methods are more commonly used for 5hmC assessment, this section focuses only on such methods.

Genome-wide methods for detecting DNA hydroxymethylation

Genome-wide approaches are often better than candidate gene approaches when studying lesser-known epigenetic states such as hydroxymethylation. In addition, psychiatric disorders are complex behaviors that likely involve multiple genes. Currently, there are several methods. Some methods use restriction enzymes and glucosylation (the process by which β-glucosyltransferase specifically transfers a glucose unit to 5hmC, resulting in glucosylated 5hmC). One example is Aba-seq, which uses a restriction endonuclease AbaSI that selectively recognizes glucosylated 5hmC and cleaves DNA in its vicinity (within approximately 10 base pairs)[24]. Another example is Reduced Representation Hydroxymethylation Profiling, in which DNA is first digested with the enzyme MspI, which recognizes and



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Figure 1 (De)methylation cycle of cytosine. Cytosines can be modified as a result of specific enzyme activity. DNA methyltransferases produce 5-methyl cytosine, which can be further oxidized to 5-hydroxymethyl cytosine by ten-eleven translocation enzymes. Further, two oxidative derivates, 5-formylcytosine and 5-carboxylcytosine, can also be generated and converted back to a cytosine form. BER: Base excision repair; DNMTs: DNA methyltransferases; SAH: S-adenosylhomocysteine; SAM: S-adenosyl methionine TET1: Ten-eleven translocation 1; TET2: Ten-eleven translocation 2; TET3: Ten-eleven translocation 3; TDG: Thymine-DNA-glycosylase.

cleaves the 5'-CCGG sequence. 5hmCs are later glucosylated, which prevents MspI from further cleavage, so that only fragments containing 5hmC are prevented from enzymatic digestion[25].

Tet-assisted bisulfite sequencing (TAB-seq) also takes advantage of glucosylation of 5hmC. After the glucosylation step, the DNA is oxidized using Tet proteins. The glucosylated 5hmC is retained, while 5mC converts to 5-carboxylcytosine (5caC). This oxidized DNA is then treated with bisulfite conversion and polymerase chain reaction (PCR) amplification, where unmethylated cytosines and 5mC (now 5caC) are converted to thymine, while glucosylated 5hmCs become cytosines. TAB-seq is more appropriate when only the 5hmC content is of interest[26].

A more complex method is a variant of bisulfite sequencing called oxidative bisulfite sequencing (oxBs-seq). In oxBs-seq, the sample of interest is divided into two parts; one part is subjected to bisulfite treatment, and after PCR amplification both 5hmC and 5mC are observed as cytosines. The second part of the sample is oxidized before bisulfite treatment, converting 5hmC to 5fC and after PCR amplification to thymine, with 5mC seen as cytosines. This parallel sequencing of the same sample allows accurate detection of 5hmC but increases the price because very high coverage is required[27].

Immuno-dot blot methods use antibodies that can recognize 5-hydroxymethylcytosine. A major advantage of these methods is their relative simplicity in terms of wet-lab work. They provide information on global DNA hydroxymethylation throughout the genome and provide a single numerical measure. The results do not provide detailed information on the state of hydroxymethylation in specific genomic regions, but can be used to provide a comprehensive overview of the state of hydroxymethylation in the genome[28]. A more complex immune approach uses the combination of hydroxymethylation-specific antibodies with next generation sequencing. In antibody-based methods such as hydroxymethylated DNA immunoprecipitation sequencing, DNA is cut into short fragments. Using antibodies against hydroxymethylation, only the hydroxymethylated DNA is isolated from the mixture of DNA fragments. A library is created from the purified DNA fragments and sequenced using next-generation sequencing[29]. Compared with oxBs-seq, this is a less costly option. It does not provide base pair resolution, but a resolution of a few hundred base pairs is usually sufficient for regional overview and gene identification[23,30].

Nanopore technologies is a third-generation (long-read) sequencing approach. Compared with the commonly used Illumina approach of "sequencing by synthesis", sequencing with Nanopore techno-

logies is based on small changes in current. During sequencing, DNA strands pass through protein nanopores about 1.8 nanometers in diameter embedded in a polymer membrane. As DNA strands enter the pore, the current changes according to the DNA bases that are inside the pore (about 6 DNA bases at a time). This also allows detection of epigenetic changes[31]. The advantage of this method is that it provides genome-wide information, while long reads (up to several Mb = 10^6 base pairs) allow detection of rare variants/deletions/insertions/repetitive regions as well as epigenetic DNA changes (both DNA methylation and hydroxymethylation), all in a single sample. This reduces the possibility of biological and technical errors. Although the price per sample is high (the total cost is nearly € 1000 per sample), it allows a much more detailed examination of a sample[32].

CURRENT OVERVIEW OF DNA HYDROXYMETHYLATION STUDIES AND PSYCHIATRIC DISORDERS

As mentioned above, psychiatric disorders are multifactorial disorders influenced by both genetic and epigenetic factors. As epigenetic mechanisms show a high degree of tissue specificity, the best biological source (tissue or organ) for studying psychiatric disorders is therefore the brain. Studies often focus on brain regions related to emotional and behavioral responses, and cognitive and executive control functions. These often-studied regions include the limbic system (hippocampus) and the prefrontal cortex (PFC) (Brodmann area 9 in the dorsolateral PFC)[33,34]. Since the brain is not accessible during life, other peripheral, more easily accessible tissues, such as blood, are often included in studies of psychiatric disorders as well. In the following paragraphs the available studies on DNA hydroxymethylation are summarized, with more technical data presented in Table 1.

DNA hydroxymethylation and suicidal behavior

In the field of suicidal behavior only two studies have been published that examined the pattern of DNA hydroxymethylation in suicide completers. Gross *et al*[35] examined DNA hydroxymethylation levels in PFC of male suicide completers with MDD. Compared to the control group, no global changes in DNA hydroxymethylation distribution were observed. They did however observe 550 differentially hydroxymethylated CpG sites in the genome. Lutz *et al*[36] included DNA hydroxymethylation analysis of opioid related genes in three brain regions (anterior cingulate cortex, thalamus and anterior insula). Suicide completers who experienced child abuse showed decreased level of DNA hydroxymethylation, while suicide completers with no history of child abuse did not. The decrease in DNA hydroxymethylation may therefore be a mark of child abuse.

DNA hydroxymethylation and SZ

SZ is a complex, multifactorial disease that causes psychosis. Psychotic symptoms include changes that affect personal and occupational life, *e.g.*, positive symptoms such as hallucinations, delusions, thought and movement disorder, and negative and cognitive symptoms[37]. SZ manifests in late adolescence or early adulthood. Due to psychotic symptoms, SZ is also accompanied by an elevated risk of suicide, which reduces life expectancy for people developing it[38].

Factors that contribute to the development of SZ are both genetic and environmental[39]. Large-scale GWAS has highlighted a large number of variants with small effects which are highly heterogeneous between individuals. The importance of environmental factors is studied through epigenetics. Genome-wide approach and specific candidate gene studies have shown differences in DNA methylation and histone modifications in schizophrenic patients. Associated genes are involved in axon and dendrite extension, oligodendrocyte differentiation, regulation of GABAergic transmission, metabolism of dopamine, and glutamate and serotonin receptors[40].

Candidate gene studies have shown hyper- and hypo-methylated genes in brain tissue in concordance with studies on peripheral tissue (whole blood, peripheral leukocytes, or saliva). However, the results of DNA methylation studies are not always similar between male and female patients. Moreover, many interesting results from DNA methylation studies have pushed interest toward DNA hydroxymethylation. Even though there are not as many studies investigating hydroxymethylation, and much more work needs to be done, some interesting results have been obtained[40].

The level of 5mC is increased in both male and female SZ patients, but 5hmC level in peripheral blood is increased in males and decreased in females compared to controls. Furthermore, 5mC globally increased with age in all participants (schizophrenic and controls), but there was no significant correlation with age for the 5hmC level[41]. An increased level of 5hmC was also reported in the promoter of the *GABRB2* gene in peripheral white blood cells of patients with SZ compared with controls. Furthermore, they found a correlation between promoter 5mC and 5hmC levels, with single nucleotide polymorphisms in patients with SZ. Heterozygous (C/A) genotypes of rs72815526 were correlated with increased 5hmC levels whereas heterozygous (C/T) genotypes of rs3811997 were correlated with decreased 5mC levels[42].

Table 1 Detailed data on DNA hydroxymethylation studies and psychiatric disorders

Ref.	Studied disorder	Subjects	Tissue	Method	Main results
Gross *et al* [35], 2017	Suicidal behavior/major depressive disorder	Subjects with major depressive disorder; *n* = 19 and psychiatrically healthy controls; *n* = 19	Prefrontal cortex	AbaSI sequencing	No differences in 5hmC density across the genome. Site-specific differential hydroxymethylation in the depressed brain
Lutz *et al* [36], 2018	Suicidal behavior	Suicide completers (severe child abuse history); *n* = 30, suicide completers (no child abuse history); *n* = 30 and control group; *n* = 34	Anterior insula	Targeted oxidative bisulfite sequencing	Childhood abuse in the past is associated with decreased hydroxymethylation of Kappa Intron 2
Jiang *et al* [41], 2017	Schizophrenia	Schizophrenic subjects; *n* = 264 and controls; *n* = 221	Peripheral blood	Dot blot-based measurement	5hmC levels increased in male SZ patients but decreased levels in female SZ patients
Zong *et al* [42], 2017	Schizophrenia	Schizophrenic subjects; *n* = 279 and controls; *n* = 256	Peripheral white blood cells	HpaII/MspI restriction-based EpiMark 5hmC/5mC Analysis Kit followed by qPCR	5hmC increased in the promoter of the *GABRB2* gene; correlation between heterozygous genotype rs72815526 (C/A) and 5hmC levels increased
Gavin *et al* [44], 2012	Schizophrenia and bipolar disorder	Schizophrenic subjects; *n* = 15, subjects with bipolar disorder; *n* = 11, and controls; *n* = 15	Parietal cortex (Brodmann area 39-40)	hMeDIP	5hmC increased at the promoter IXabcd of the *BDNF* gene
Dong *et al* [45], 2012	Schizophrenia and bipolar disorder	Schizophrenic subjects; *n* = 10, subjects with bipolar disorder; *n* = 9, and controls; *n* = 11	Inferior parietal lobule	Immuno-dot-blot analysis	5hmC increased at the *GAD67* gene at -537 to -415, and -145 to +21; 5hmC increased at the *BDNF* IXabcd gene at -60 to +50 not within *BDNF* exon IXd at +1185 to +1305
D'Addario *et al*[57], 2019	Obsessive compulsive disorder	Obsessive compulsive disorder; *n* = 35, and controls; *n* = 32	Peripheral blood mononuclear cells	Bisulfite conversion or oxidative bisulfite conversion, followed by pyrosequencing	*BDNF* hydroxymethlation decreased at promoter exon I; no changes in promoter exon IV and IX
Clark *et al* [60], 2022	Substance use disorder	Alcohol use disorder; *n* = 25, and controls; *n* = 25	Prefrontal cortex (Brodmann area 10)	Selective chemical labelling and enrichment of hmC (hMe-Seal)	*BAIAP2* hydroxymethylation increased

5hmC: 5-hydroxymethycytosine; SZ: Schizophrenia; 5mc: 5-methylcytosine; qPCR: Quantitative real-time polymerase chain reaction; BDNF: Brain-derived neurotrophic factor.

DNA hydroxymethylation and BP

BP is a chronic psychiatric disorder characterized by unusual shifts in mood, energy, activity levels, and concentration. Impulsive reckless behavior leads to an increased risk of suicide[43]. Since SZ and BP are both psychoses, some studies have been made on a combined group of people with SZ and BP[44,45].

A number of studies address DNA methylation in patients with BP but just two have investigated hydroxymethylation where patients with BP were included in the study alongside patients with SZ, forming a combined group of psychotic illnesses. In a study made on parietal cortical samples from psychotic patients (Brodmann area[39,40]), an increase in 5mC and 5hmC was observed at the promoter IXabcd of the brain-derived neurotrophic factor (*BDNF*) gene. This result was also associated with reduced transcription of the *BDNF* gene[44]. In another study on the inferior parietal lobule of psychotic patients increased expression of the *TET1* gene was detected. Consistent with the increase of expression the *TET1* gene, there was an increased level of 5hmC. Specifically, higher 5hmC levels were observed at the glutamate decarboxylase 67 gene at positions -537 to -415 and -145 to +21 in psychosis patients *vs* control. There was also an increase in 5hmC at the BDNF IXabcd gene at position -60 to +50 in psychosis patients *vs* control, but not within *BDNF* exon IXd at +1185 to +1305[45].

DNA hydroxymethylation and MDD

MDD is the psychiatric disorder that contributes the most to the global health burden, and is the primary cause of disability globally. The environmental factors that increase the risk of MDD the most are stress and exposure to adverse life events, meta-analyses and genome-wide studies have shown that genetic factors also contribute to its development, contributing about 40%[46].

The DNA methylation studies were summarized in a recent systematic review[47]. Out of 67 studies 61 were performed on blood samples and thus lacked information on the status of DNA methylation in the central nervous system. Among the already well-established genes, hypermethylation of BDNF and the serotonin transporter gene showed association with depression on general or MDD. Results of other genes showed mixed results[47].

Only two studies on hydroxymethylation in MDD have been reported so far the studies by Gross *et al* [35] and Lutz *et al*[36] mentioned previously. In both studies the brain tissue of subjects with MDD who died due to suicide was used, making it difficult to link the observed differences to MDD alone.

Although studies in human are lacking, three studies on mice strain C57BL/6 have been reported, all investigating the TET enzymes. Feng *et al*[48] applied chronic stress, and determined decreased levels of expression of *TET1* in the nucleus accumbens in stress-susceptible mice. In a *TET1* knockout genes related to the immune system were demonstrated to be the most highly dysregulated. Zhang *et al*[49] examined the *TET2* knockout animals, and identified some hydroxymethylated regions that overlapped with known depression-associated loci. They also showed abnormal translocation of TET2 protein from the cytosol to the nucleus in chronic stress induced mice. Cheng *et al*[50] showed that chronic restraint stress induced depression-like behavior in mice and reduced hydroxymethylation of the PFC. Knocking out *TET1* resulted in resistance to chronic restraint stress, while a knockout of *TET2* increased the susceptibility to chronic restraint stress[50]. The above results indicate that hydroxymethylation exhibits dynamic changes in response to stress-induced stimuli, resulting in changes of epigenetically regulated gene expression.

DNA hydroxymethylation and OCD

OCD is a psychiatric disorder characterized by obsessions and compulsions of various natures and degrees, and is in the majority of cases accompanied by at least one comorbid psychiatric disorder, most commonly MDD[51]. OCD is a heritable disorder with a polygenic background. Candidate gene and genome-wide studies suggest that the serotonergic, dopaminergic, and glutamatergic systems, and the interaction between them, contribute to the risk of the OCD[52]. Important contributing environmental factors are perinatal complications, childhood trauma, reproductive cycle events, and stressful life events[51].

Epigenetic studies of OCD have mostly investigated DNA methylation. Using the genome-wide approach, covering over 485000 CpG sites, genes previously associated with OCD were detected[53]. With the candidate gene approach the oxytocin receptor and serotonin transporter genes were interrogated. The results were mixed, showing both higher and lower level of methylation in OCD patients compared to controls[54-56].

In the context of the candidate gene approach *BDNF* methylation and hydroxymethylation have also been analyzed. Expression of *BDNF* in peripheral blood mononuclear cells demonstrated broad association with OCD, showing an increase in gene expression, as well as significant correlation of both lower methylation and higher hydroxymethylation at promoter exon I[57]. The results were replicated on saliva samples, showing lower levels of methylation in OCD compared to controls[2].

DNA hydroxymethylation and substance use disorder

Substance use disorder (SUD) is a mental disorder with a range of symptoms from moderate to severe. The most severe SUD is addiction. SUD affects a person's brain and behavior, which leads to the uncontrollable use of substances, such as drugs, alcohol, and medications[58]. It is common that people with SUD are also diagnosed with mental disorders and vice versa. Common mental disorders that co-occur with SUD are depression, BP, attention-deficit hyperactivity disorder, psychotic illness, borderline personality disorder, and antisocial personality disorder[59]. There are three suggestions for their joint occurrence. Firstly, common risk factors might contribute to SUD and other mental disorders; secondly, mental disorders can contribute to substance use and SUD; thirdly, substance use and SUD contribute to the development of other mental disorders[58]. It is estimated that there is a 40%-60% genetic contribution to vulnerability for developing SUD. For example, genetic vulnerability can be seen through changes in the degradation of the consumed, inhaled, or injected substance[59]. Moreover, there are also environmental factors that work through the epigenome[60].

There are several studies investigating 5hmC changes in the brains of people with SUD[61]. Clark *et al* [60] showed a difference in 5hmC of the BAIAP2 gene in the PFC from people with alcohol use disorder (AUD)[60]. One study showed differential expression of TET1 in the cerebellum of people with AUD, but no differences in 5hmC in the promoter of GABAergic genes[62]. More studies of SUD were made on model organisms, where they found 5hmC alteration after cocaine and methamphetamine administration in the nucleus accumbens[48,63,64], and a higher global 5hmC level was observed in nucles accumbens after ethanol administration[65].

CONCLUSION

In treatment of psychiatric disorders there is currently only a limited selection of validated biomarkers in use (*e.g.*, electrophysiological biomarkers, neuropsychological biomarkers, brain imaging biomarkers, blood biomarkers), while molecular-genetic markers particularly have not yet entered the routine practice. The selection of treatment is based on clinical interview. In many cases patients do not respond to the medication prescribed or their treatment is changed too quickly due to side effects, since the response to the same medication can be highly variable among patients. Thus, the screening of a

patient's genetic background could improve the selection of a suitable medicine(s) based on an individual's genetic background, taking into account pharmacokinetic and pharmacodynamics parameters. These specific differences in gene makeup have been tested in genes responsible for drug metabolism, however other genes also show changes that can significantly affect the development of disease. Shortly after the beginning of the millennium the human genome was sequenced, initiating exponential growth of genome-wide studies that continues until today. It has become evident that psychiatric disorders are polygenic, and that changes in gene sequences (*e.g.*, single nucleotide polymorhpisms, copy number variations) contribute small effects which result in the development of the disorder, also through genetic pleiotropy and epistasis. However, the results of these studies have been mixed, identifying different genes, so no particular genetic locus can be linked to a given psychiatric disorder and used as a biomarker. Since psychiatric disorders show a significant proportion of environmental risk factors, the study of epigenetics has become an important approach to linking genetics with environmental effects, and might therefore provide applicable biomarkers for diagnosis and treatment.

The majority of epigenetic studies have interrogated DNA methylation as the prime epigenetic mark, but again these have produced mixed results at the level of genome-wide analysis, while the candidate gene approach has confirmed the importance of genes involved in neurotransmission and neurotrophic growth factors. Since the development of psychiatric disorders stems from disrupted signaling in the brain DNA hydroxymethylation, which can affect neuroplasticity and neurotransmission, has become an interesting research field. To date not many studies are available, as this area develops, and joint studies on transcriptional regulation are carried out, we expect to be able to improve effects evoked by pharmacotherapy with beneficial effects on patients' health.

As is the case with genetic biomarkers, epigenetic biomarkers are not currently useful in a clinical setting, and many gaps remain in the understanding of their function. To advance our understanding of potential biomarkers, more studies simultaneously interrogating the status of the brain and peripheral tissue such as blood or even saliva are needed. Biomarkers showing good overlap between different tissue types could become key elements of validation studies on bigger, clinically well-defined cohorts, helping to discern the molecular mechanisms of psychiatric disorder development, diagnosis and treatment.

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MINIREVIEWS

Psychological trauma, posttraumatic stress disorder and trauma-related depression: A mini-review

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Abstract

There are various types of traumatic stimuli, such as catastrophic events like wars, natural calamities like earthquakes, and personal trauma from physical and psychological neglect or abuse and sexual abuse. Traumatic events can be divided into type I and type II trauma, and their impacts on individuals depend not only on the severity and duration of the traumas but also on individuals' self-evaluation of the traumatic events. Individual stress reactions to trauma include posttraumatic stress disorder (PTSD), complex PTSD and trauma-related depression. Trauma-related depression is a reactive depression with unclear pathology, and depression occurring due to trauma in the childhood has gained increasing attention, because it has persisted for a long time and does not respond to conventional antidepressants but shows good or partial response to psychotherapy, which is similar to the pattern observed for PTSD. Because trauma-related depression is associated with high risk of suicide and is chronic with a propensity to relapse, it is necessary to explore its pathogenesis and therapeutic strategy.

Key Words: Psychological trauma; Trauma-related depression; Reactive depression; Posttraumatic stress disorder; Antidepressant; Psychotherapy

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Core Tip: Exposure to psychological trauma may induce posttraumatic stress disorder (PTSD) and trauma-related depression. Major depression can be a progression secondary to PTSD. Both trauma-related depression and PTSD show good response to psychotherapy or prazosin, but a poor response to conventional antidepressants, suggesting that trauma-related depression should have different pathological mechanisms, like energy metabolism deficiency. It is necessary to explore the pathogenesis of and therapeutic strategy for PTSD and trauma-related depression.

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INTRODUCTION

Psychological trauma is a stressful event that causes distress that exceeds an individual's ability to integrate the emotions and cognitions involved in the experience[1]. Its occurrence is unexpected and uncontrollable, often exceeding people's coping resources and making them feel powerless, helpless, and fearful. Besides natural disasters and wars, psychological trauma also encompasses various forms of physical and emotional abuse or neglect, sexual abuse, bullying, or household dysfunction experienced throughout one's entire lifespan[2].

Psychological trauma has attracted attention when the veterans returned from the Vietnam War. Although their lives have been restored, the scenarios on the battlefield always reappear and flash up in their brain every day accompanied by fragmentary memories, sleep disorders, nightmares, unstable moods, and anhedonia[3]. For the evaluation and intervention of the veterans' psychological crisis, posttraumatic stress disorder (PTSD) was first inserted in the third edition of Diagnostic and Statistical Manual of Mental Disorders in 1980[4].

Traumatic events increase not only the risk of PTSD but also depression. Trauma-related depression, which meets the criteria of major depressive disorder, can be caused directly or indirectly by psychological trauma. Previous studies showed that 61% of patients with first-episode depression and 51% with recurrent depression reported childhood or recent trauma, including adverse childhood experiences[5], recent life events[6], and occupational stressors[7]. While the pathological mechanism remains unclarified, trauma-related depression has attracted more attention because of its prolonged duration and resistance to conventional antidepressants. However, patients with trauma-related depression have a full or partial response to psychotherapy, like PTSD. Since trauma-related depression is at a high risk of suicide and is prone to relapse and be chronic, it is essential to explore the pathogenesis, therapeutic strategy, and causal relationships between psychological trauma, PTSD, and trauma-related depression. In this article, we will review the clinical characteristics of and relationship between PTSD and trauma-related depression, and their therapies.

TYPES AND CHARACTERICS OF TRAUMA

Terr[8] divided childhood trauma into type I and type II trauma (Table 1)[8,9] according to trauma characteristics. Type I trauma includes fully detailed memories, "omens", and misperceptions (such as a car accident) and has characteristics including: (1) The time of trauma formation is short or at one time; (2) trauma may occur in different stages of childhood and adulthood; (3) the duration of trauma is not long, usually within three months; and (4) some heal naturally, some benefit from treatment, and some transform into type II. Type I trauma may lead to acute stress disorder (ASD), PTSD, and adjustment disorders. Among these disorders, PTSD is the most harmful. The diagnostic requirements of PTSD include re-experiencing traumatic events, avoidance, increased sensitivity or alertness, and functional impairment.

Type II is complex trauma, including denial and numbing, self-hypnosis and dissociation, and rage, which repeatedly occurs in childhood and lasts for a long time, such as physical and emotional abuse and neglect. Its characteristics include a long time to form and a broad impact on an individual's body and mind. The trauma may occur in different stages of childhood development or adult life. In general, type II trauma presents complex and diverse symptoms and will not heal naturally. 25% to 30% of type II trauma may evolve from type I trauma[10]. Compared with type I, type II trauma has a more severe impact on individuals. It also significantly differs from type I trauma in terms of its symptoms, neuroimaging findings, treatments, and prognoses. Furthermore, it also often leads to complex PTSD (CPTSD)[11].

Table 1 Characteristics of Type I and Type II trauma

Characteristics	Type I	Type II
Resource	Disaster or accident	Abuse or violence or neglect
Onset	Acute onset	Acute or insidious onset in childhood
Duration	Sudden, transient	Repeated, long-lasting
Outcome	Be healed or develop to Type II	Be scarred or protracted
Manifestation	Re-experience, avoidance, alertness, *etc.* (take PTSD as an example)	PTSD symptoms, disorders in self-organization, disassociation
Mental disorders	Acute stress disorder, PTSD, adjustment disorder	CPTSD, adjustment disorder, Dissociative/conversive disorder

PTSD: Posttraumatic stress disorder; CPTSD: Complex posttraumatic stress disorder.

The term "complex PTSD" was proposed by Herman[11] to describe the repeated and long-term symptoms experienced by survivors of trauma, including changes in emotional regulation, consciousness, self-perception, and interpersonal relationships. This disorder can result from a single severe traumatic event or multiple chronic traumas that are difficult or impossible to escape, such as childhood abuse, domestic violence, torture, and imprisonment. The diagnosis of CPTSD in International Classification of Diseases 11th edition (ICD-11)[9] requires not only meeting the diagnostic criteria of PTSD but also evidence of disorders in self-organization, including affective dysregulation, negative self-concept, and disorders in relationships.

There is additional type of trauma called chronic unpredictable mild stress (CUMS), which has been used to model depressive symptoms in rodents[12]. Long-term (> 3 wk) exposure to a series of mild but unpredictable stressors can make animals depressive, which simulates a depressive state of human beings after encountering the stressors in the real world. However, there have been few clinical studies on CUMS thus far[13].

TRAUMA AND STRESS RESPONSE

The impact of trauma depends not only on the traumatic event itself but also on the individuals' perceptions, psychological defense mechanisms, and whether the support system is timely and sufficient. Although genetic heritability is one of the risk factors for the development of PTSD or major depressive disorder (MDD) in the population with traumas, a genetic factor may be less important as trauma exposure increases, that is, high levels of trauma are likely to lead to PTSD and MDD[14].

From the perspective of psychiatric phenomenology, traumatic events may lead to a series of nonspecific mental and behavioral symptoms of post-trauma reaction. The impact of trauma on an individual's mental state is mainly determined by the trauma's intensity, duration, and age. According to the theory of the classical response to stress[15], stress reaction can be roughly divided into alarm, resistance, and exhaustion stages[16]. In the alarm stage of post-trauma condition, a stress reaction may manifest a "fight or flight" response by activating the sympathetic nervous system to release catecholamine. If stress reaction is insufficient, ASD will occur. After the acute stage comes the resistance stage. This stage involves adjustment to the persistent trauma or the after-effects of traumatic events *via* the activation of the hypothalamus–pituitary–adrenal (HPA) axis and promotion of endogenous glucocorticoids function to maintain the internal environment. If the stress reaction is insufficient, the manifestations of PTSD will appear.

If the trauma is too intense or prolonged, Individuals will encounter the exhaustion stage by excessive mobilization of the sympathetic nervous system and HPA axis, and manifests maladjustment or trauma-related depression (reactive depression). Therefore, multiple traumatic events can have cumulative detrimental effects on mental health of the victims[17], manifesting depressive symptoms such as negative emotions, guilt, shame, self-blame, social withdrawal, or social isolation. They can also become irritable, aggressive, violent, and of self-injury or suicidal behaviors, or have persistent dissociative symptoms and acoustic and visual hallucinations similar to those that occur in psychosis[18, 19]. Individuals with post-trauma reactions are often diagnosed with depression or bipolar depression with or without psychotic symptoms or borderline personality disorder according to the ICD-11 or the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)[20].

PTSD AND TRAUMA-RELATED DEPRESSION

Relationship between PTSD and trauma-related depression

Studies have shown that collective trauma caused by earthquakes and plagues may lead to collective emotions accompanied by pro-social behaviors, thus reducing the adverse effects of traumatic events on individuals[21]. However, suffering from interpersonal trauma (individualized trauma) such as abuse, neglect, or sexual violence often brings negative consequences which are easily internalized, become chronic and gradually develop into "trauma mode" as Piaget referred to[22], which manifests as persistent depression, negative cognition, negative self-concept, and self-injury/suicide[23].

ASD usually occurs within minutes or hours after a severe traumatic event. The symptoms are transient, usually relieved within days or a week. Therefore, PTSD is the most common lasting and harmful stress response to trauma and it is dominated by negative emotions such as anxiety, fear, irritability, and depression. The onset of PTSD usually occurs one month or several years after traumatic events. PTSD and depression often occur comorbidly. As a result of a meta-analysis (k = 57 studies; n = 6670 participants), 52% of individuals with PTSD had comorbid MDD[23]. In addition, a number of overlapping symptoms were reported. Although it is sometimes challenging to differentiate, PTSD and MDD are two significantly different diseases.

Although the depressive symptoms present in PTSD can predict the occurrence and severity of depression, some scholars, such as Freedman *et al*[24] and Bleich *et al*[25] argue that there is no chronological progression from PTSD to MDD. However, many studies support the continuity between PTSD and MDD[26,27]. PTSD can lead to affective disorder[16], significantly increasing the risk for the first-onset of major depression[28].

The COVID-19 pandemic caused long-term psychological impacts on people, like insomnia, anxiety, depression, and burnout syndrome, which has raised public health concerns globally. Burnout is a state of physical or mental stress resulting from prolonged exposure to job stressors. Burnout prevalence differs in different specialties. Studies have shown that after a high workload or prolonged contact with patients, nearly one-third of healthcare workers met the clinical level of exhaustion and manifested anxiety, irritation, fatigue, depression, depersonalization, and PTSD[29,30]. A 1-year observational study showed that the prevalence of burnout and anxiety was similar at 3 mo (52% *vs* 51%) and 12 mo (23% *vs* 23%), while the prevalence of PTSD was higher than that of depression at both 3 mo (23% *vs* 11%) and 12 mo (11% *vs* 6%)[31].

The prevalence of depression and PTSD-like symptoms in adolescents increased significantly during the pandemic period of COVID-19[32,33]. During the COVID-19 pandemic, the comorbidity prevalence of PTSD and depression was about 50%[34]. However, a remote telephone interview revealed that the prevalence of PTSD and depression in patients who recovered from COVID-19 was 56.9% and 29.0%, respectively[35]. It indicates that PTSD symptoms are the main symptoms during or at the beginning of traumatic events.

In a survey of the elderly, the lifetime prevalence and 12-mo prevalence of sexual violence are 44% and 8%, respectively, while the lifetime prevalence of depression, anxiety, and PTSD are 27%, 26%, and 6%, respectively[36]. It indicates that the long-term effects of traumatic events on individuals are mainly depressive symptoms, and the patients might be diagnosed with major depressive disorder according to DSM-5 or ICD-10. Because this type of depression is associated with psychological trauma(s), it is often resistant to the treatment and much harmful.

Treatment and potential mechanism of PTSD and trauma-related depression

Trauma-related depression is caused by intense and persistent frustration or other psychological conflict factors. It may be considered reactive depression (stress-induced depression) and different from endogenous (biogenic) depression. Reactive depression and endogenous depression were proposed by the German psychiatrist Kurt Schneider in 1920[37] in trying to classify depression by its etiology. This classification enjoyed broad acceptance[38] up to the introduction of DSM-IV in 1994[39]. Since then, psychiatrists and scholars have returned to the principle of phenomenological description of mental disorders. For instance, if a patient has clinical manifestations that meet the descriptive criteria for depression, the patient will be uniformly diagnosed with depression without emphasizing its etiological classification, which makes the diagnosis and intervention much easier. The etiology of different depression types seemed less important, particularly since the discovery of tricyclic antidepressants and the establishment of a monoamine-based hypothesis[40].

However, since 1994 and even more since the COVID-19 pandemic, patients with reactive depression have increased markedly[41]. The poor efficiency of conventional antidepressants in reactive depression has again drawn attention to psychological trauma and "reactive depression", particularly depression with childhood trauma. Studies[42,43] have confirmed that depression related to trauma (especially childhood trauma) is very complex in clinical manifestations and many other aspects, such as neurobiological factors, treatment response and prognosis.

Childhood trauma or a recent traumatic event is an important precipitating and perpetuating factor of depression in adolescents and elderly patients[36,43]. Severe psychological trauma can also lead to PTSD or CPTSD with comorbid depression. For example, more than 50% of PTSD patients have

Table 2 Studies investigating the therapy on major depressive disorder patients with childhood trauma or recent trauma

Ref.	Study/review	Details	Tools	Results
Nemeroff *et al*[47], 2003	RCT	681 MDD patients with childhood trauma were assigned to nefazodone, CBASP, or combination	HRSD24	For those with childhood trauma, psychotherapy alone was superior to antidepressant monotherapy
Asarnow *et al*[52], 2009	RCT	334 youth failed in an adequate SSRI trial were randomized to 12 wk with an alternative SSRI, an alternative SSRI + CBT, venlafaxine, or venlafaxine + CBT	CDRS-R, CGI-I	The CBT or combined treatment was superior to medication alone
Nanni *et al*[50], 2012	meta-analysis	10 clinical trials of 3098 MDD subjects with childhood trauma were analyzed based on depression course: recurrence or persistence	CIDI, PSE, SCAN, MINI or HAMD	Childhood maltreatment was associated with lack of response to treatment and lack of remission (OR = 1.43, 95%CI: 1.11-1.83)
Williams *et al*[48], 2016	Cohort study	1008 MDD and 336 healthy controls were treated with escitalopram, sertraline or venlafaxine for 8 wk	QIDS_SR16, HRSD17	Below 7 yr of age predicted poorer outcomes, and 4-7 yr the poorest
Yrondi *et al*[51], 2019	Cohort study	In 291 TRD patients, 135 (52.7%) were available at 1-year follow-up	QIDS_SR, MADRS	Baseline CTQ scores had a significant influence on remission at 1 year [χ^2 (1) = 5.57; P < 0.05]
Christensen *et al*[6], 2020	Cohort study	61% of subjects (1113/1811) reported trauma history, and were treated with vortioxetine (5-20 mg/d) or placebo for 8 wk	MADRS, CGI-I	Subjects with trauma with placebo were more likely to relapse than with vortioxetine
Menke *et al*[55], 2021	Cohort study	150 in-patients of MDD were recruited in the 4-wk antidepressant trial, 68 with multiple childhood trauma (*i.e.* ≥ 3) and 59 with ≥ 3 severe recent life events	HRSD21	Severe recent life events were associated with a poor response to antidepressants (F = 7.456; df = 1; P = 0.008), These effects may not be observed with childhood trauma

RCT: Randomized controlled trial; MDD: Major depressive disorder; CBASP: Cognitive behavioral analysis system of psychotherapy; HRSD24: Hamilton rating scale for depression-24 items; SSRI: Selective serotonin reuptake inhibitor; CBT: Cognitive-behavioral therapy; CDRS-R: Children depression rating scale-revised; CGI-I: Clinical global impression–improvement; CIDI-C: Composite international diagnostic interview-core version; PSE: Present state examination; SCAN: Schedules for clinical assessment in neuropsychiatry; MINI: The MINI-international neuropsychiatric interview; HAMD: Hamilton depressive scale; OR: Odds ratio; 95%CI: 95% confidence interval; QIDS_SR16: The 16-item self-report versions of the quick inventory of depressive symptomatology; HRSD17: Hamilton rating scale for depression-17 items; TRD: Treatment-resistant depression; QIDS_SR: Self-report versions of the quick inventory of depressive symptomatology; MADRS: The Montgomery-Asberg depression rating scale; CTQ: The Childhood trauma questionnaire; HRSD21: Hamilton rating scale for depression-21 items.

comorbid depression[34]. Psychological trauma may affect the individual's response to antidepressants, clinical outcomes, and function. Regarding the treatment of PTSD, paroxetine, sertraline, fluoxetine, and venlafaxine are recommended, however, the efficiency of selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors in PTSD is comparably low (only about half as strong)[44]. Psychotherapy is the treatment of choice for PTSD, including cognitive behavior therapy (CBT), prolonged exposure, and eye movement desensitization and reprocessing (EMDR)[45].

The treatment of trauma-related depression, particularly in patients with childhood trauma, has been extensively studied (Table 2). Previous studies have shown that various childhood abuses is unfavorable to the treatment, and the poor response is significantly related to childhood abuse[46-48], particularly trauma that occurred before the age of 7 years. Even after 8 wk of therapy with antidepressants, there was no remission. Moreover, there was a high risk of recurrence[5,48]. Meanwhile, childhood trauma is also an important risk factor for suicidal ideation and the increased severity of refractory depression[49-51]. However, although patients with chronic depression after trauma have a comparatively good response to the psychotherapy with EMDR[47]. Asarnow *et al*[52] found that patients of refractory depression with a history of abuse have a significantly lower response to CBT than those without abuse. Shirk *et al*[53] believed that trauma-focused cognitive behavioral therapy (TF-CBT) could significantly improve depressive symptoms. A meta-analysis[54] showed that TF-CBT and EMDR are beneficial in alleviating the traumatic experience, depression, and anxiety of patients with PTSD. It was found that psychotherapy has better compliance than psychopharmacological therapy. Therefore, it is suggested that psychotherapy should be introduced in the early stage of the treatment of trauma-related depression[55].

Taken together, for the patients with trauma-related depression, the symptomatology is more complex; the suicide rate is higher[49]; the clinical condition is more prone to be chronic, and the response to antidepressant is poorer[5,42,47,48]. Therefore, it is speculated that trauma-related depression may have different biological mechanisms compared to other depressed patients[56,57].

Compared with classic depression, there are few studies on the underlying neurobiological mechanisms of trauma-related depression. It was previously thought that the occurrence of PTSD or chronic PTSD was related to noradrenergic dysfunction[58] or cytokines[57]. However, in recent years, we have learned by the CUMS model that energy metabolism disorder might play an important role[59-61].

Although the etiological mechanisms underlying PTSD or trauma-related depression are not known in detail, the efficacy of certain therapies may be indicative of existing pathomechanisms[62]. For example, in a case study, it was reported that low-dose prazosin led quickly to rapid improvement in depressive symptoms, including cognitive function in a therapy-resistant depressive patient with comorbid chronic PTSD[63]. The patient had previously received antidepressants that work *via* serotoninergic, noradrenergic, and dopaminergic mechanisms as well as several sessions of modified electroconvulsive therapy but did not benefit from these treatments, suggesting that prazosin may have acted by different pharmacological mechanisms from monoamine hypothesis[64]. This observation might turn out to be important in order to explore the pathogenesis of PTSD and trauma-related depression[65].

However, there is also a meta-analysis[50] has showed that, for adult depressive patients with childhood abuse, the effectiveness of antidepressant drugs alone, and psychotherapy alone, combined therapy is not satisfactory. In the same sense, some PTSD patients still have poor responses to psychotherapy. Therefore, we need to explore new treatment methods to improve the prognosis of PTSD patients with comorbid depression. For this purpose, it is necessary to expand our knowledge of the pathogenesis of trauma-related depression.

CONCLUSION

Exposure to psychological trauma may induce PTSD and trauma-related depression. Major depression can be a progression secondary to PTSD. Both trauma-related depression and PTSD show good response to psychotherapy or prazosin, but a poor response to conventional antidepressants, suggesting that trauma-related depression should have different pathological mechanisms, like energy metabolism deficiency. It is necessary to explore the pathogenesis of and therapeutic strategy for PTSD and trauma-related depression. Although we reviewed detailed features of trauma-related depression and PTSD, the relationship between them is ambiguous. In this article, one weakness is the limited discussion of the pathogenesis of trauma-related depression and PTSD, and the etiological roles in the pathogenesis.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Acupuncture at Back-Shu point improves insomnia by reducing inflammation and inhibiting the ERK/NF-κB signaling pathway

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Abstract

BACKGROUND

Insomnia is a disease where individuals cannot maintain a steady and stable sleep state or fail to fall asleep. Western medicine mainly uses sedatives and hypnotic drugs to treat insomnia, and long-term use is prone to drug resistance and other adverse reactions. Acupuncture has a good curative effect and unique advantages in the treatment of insomnia.

AIM

To explore the molecular mechanism of acupuncture at Back-Shu point for the treatment of insomnia.

METHODS

We first prepared a rat model of insomnia, and then carried out acupuncture for 7 consecutive days. After treatment, the sleep time and general behavior of the rats were determined. The Morris water maze test was used to assess the learning ability and spatial memory ability of the rats. The expression levels of inflammatory cytokines in serum and the hippocampus were detected by ELISA. qRT-PCR was used to detect the mRNA expression changes in the ERK/NF-κB signaling pathway. Western blot and immunohistochemistry were carried out to evaluate the protein expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB.

RESULTS

Acupuncture can prolong sleep duration, and improve mental state, activity, diet

volume, learning ability and spatial memory. In addition, acupuncture increased the release of 1L-1β, 1L-6 and TNF-α in serum and the hippocampus and inhibited the mRNA and protein expression of the ERK/NF-κB signaling pathway.

CONCLUSION

These findings suggest that acupuncture at Back-Shu point can inhibit the ERK/NF-κB signaling pathway and treat insomnia by increasing the release of inflammatory cytokines in the hippocampus.

Key Words: ERK/NF-κB signaling pathway; Acupuncture; Insomnia; Inflammation; Acupuncture at Back-Shu point; Traditional Chinese medicine

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Core Tip: In this study, insomnia was a condition that was unable to maintain a stable sleep state or to sleep. Western medicine mainly uses sedative and hypnotic drugs to treat insomnia, which easy to produce drug resistance and some adverse reactions. Acupuncture has excellent efficacy and unique advantages in the treatment of insomnia. This study aimed to investigate the molecular mechanism of Back-Shu acupuncture for insomnia.

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INTRODUCTION

Insomnia is a common clinical disease. Sleeping difficulty and short sleep time are typical clinical symptoms of insomnia. Insomnia not only seriously affects patients' daily activities and work, but also leads to a reduction in their living standards. Some patients also have anxiety, depression, and other negative psychological emotions. Long-term sleep disorders can easily induce immunity and memory loss, increase the risk of cardiovascular and cerebrovascular diseases, and threaten the life and health of patients[1]. At present, sedatives, hypnotics, antidepressants, and other psychiatric drugs are mainly used to treat insomnia. However, high drug dependence and a high incidence of adverse reactions limit their clinical application[2]. Traditional Chinese medicine believes that insomnia is a type of restlessness caused by liver qi stagnation and spleen damage. Traditional Chinese medicine prescriptions and external treatment with traditional Chinese medicine have remarkable effects on this disease[3].

The pathogenesis of insomnia is still unclear and may be related to the dysfunction of neurotransmitters, inflammatory cytokines, neuroendocrine factors, melatonin, signal transduction pathways, neurotrophic factors, and intestinal flora in the brain. The ERK pathway belongs to the MAPK family and mediates various physiological and pathological processes such as cell proliferation, differentiation, apoptosis, oxidative stress, and immune inflammation. It plays an essential regulatory role in tumor pathogenesis, various inflammatory diseases, mental disorders, insomnia, and other diseases[4,5]. The ERK signaling pathway can be activated after receiving stimulation signals, which activates the downstream transcription factor NF-κB, affects the secretion of inflammatory cytokines [interleukin (1L)-1β, 1L-6, tumor necrosis factor (TNF)-α], and induces functional changes, thereby leading to insomnia and increasing the risk of chronic inflammatory diseases[6-8]. Abnormal activation of the ERK signaling pathway can also aggravate apoptosis and inflammatory injury in cardiomyocytes, leading to cardiac diseases. The administration of corresponding inhibitors can enhance myocardial reoxygenation capacity, inhibit apoptosis and the inflammatory response, reduce myocardial ischemia, and promote the recovery of cardiomyocyte function[9,10]. Clinical studies have found that acupuncture at Back-Shu point has an excellent therapeutic effect on insomnia, effectively improving depression, anxiety, memory loss, immunity decline and other clinical symptoms caused by insomnia[11]. Experimental studies have confirmed that the pathogenesis of insomnia is closely related to the ERK/NF-κB signaling pathway[12]. We hypothesize that inhibition of ERK/NF-κB signaling pathway activation may be a potential target in the treatment of insomnia.

In this study, a rat model of insomnia was established by intraperitoneal injection of p-chlorophenylalanine (PCPA). The rats were treated with acupuncture at Back-Shu point and injection of the ERK/NF-κB pathway inhibitor U0126, respectively. The sleep status, learning and memory ability, body

weight, mental state, response to external interference and other general behaviors were observed before and after treatment. The secretion levels of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α in serum and the hippocampus, and the protein expression of ERK/NF-κB signaling pathway markers were detected to verify whether acupuncture at Back-Shu point could inhibit the ERK/NF-κB signaling pathway to relieve insomnia, providing new insights for the clinical treatment of insomnia.

MATERIALS AND METHODS

Forty male specific pathogen free (SPF) Sprague Dawley (SD) rats aged 12 wk weighing 200 ± 20 g were selected and were given water and food ad libitum. The rats, purchased from Henan Laboratory Animal Center, were housed at a room temperature of 20-24 °C, and relative humidity of 40%-60%. The 40 rats were randomly divided into 4 groups: Control group (Con), model group (Model), acupuncture group (Acupuncture), and U0126 group (U0126), with 10 rats in each group. Rats in the Model group were continuously injected with PCPA suspension (1 mL/kg) by intraperitoneal injection. Rats in the Con group were injected with the same amount of normal saline. Rats in the Acupuncture group received acupuncture 7 d in advance, which was performed continuously for 7 d. Rats in the U0126 group were injected with U0126 (0.2 mg/kg/d) (Alfa Chemical, Zhengzhou, Henan, China) *via* the tail vein 7 d in advance, once a day.

Drug treatment

Ultrapure water was heated to between 30-40 °C, sodium bicarbonate powder (Tianjin Hengxing Chemical Reagent, Tianjin, China) was slowly added to prepare a 5% NaHCO3 aqueous solution, and 0.9% physiological saline was added to dilute to a weak alkaline solution (pH 7-8). PCPA was then added and sonicated for 10 h to obtain a PCPA suspension.

Evaluation of the insomnia model

Twelve hours after PCPA suspension injection on day 3, three rats were randomly selected from the Con and Model groups to receive pentobarbital sodium (45 mg/kg). The rats were placed in the supine position on the experimental table to observe the righting reflex. The disappearance of the righting reflex for 1 min was considered the sleep latency, the time to recovery was the sleep time, and the rats varus 3 times within 30 s was the end index. The sleep latency and sleep time of rats were recorded, respectively.

Acupuncture intervention

The acupoints on both sides were "Xin Yu," "Gan Yu," "PI Yu," "Fei Yu," and "Shen Yu." Xin Yu: The 5th thoracic vertebra on the lower intercostal side; Pi Yu: The 12th thoracic vertebra on the lower intercostal side; Gan Yu: The spinous process of the 9th thoracic vertebra is opened 3 mm below; Fei Yu: The 3rd thoracic vertebra on the lower intercostal side; Shen Yu: The lower side of the 2nd lumbar spine. After disinfection, the operator held a millimeter needle (0.25 mm × 15 mm) in the right hand, which was quickly inserted into the acupoint to 6 mm. The needle was retained for 10 min, and then removed. Acupuncture began at 9:00 a.m. every day for 7 consecutive days.

Morris water maze test

The rats in each group were placed into the water maze for adaptive training 1 d before the experiment. The positioning navigation experiment was used to train the learning and memory ability of the rats. The rats were placed in quadrants I, II, III, and IV daily. The test time for each quadrant was 70 s. The escape latency period was the time from placed in the water to finding the landing platform. If the platform was not found within the specified time, the animal was actively placed on the platform for 15 s to induce learning and memory ability. The SuperMaze software recorded the movement trajectory and escape latency using a camera. The spatial exploration experiment was used to evaluate the spatial memory ability of the rats. The rats were placed in the water from the contralateral side of quadrant III and allowed to freely explore for 60 s. The SuperMaze software recorded the movement trajectory of the rats using a camera.

Enzyme-linked immunosorbent assay (ELISA)

After the last behavioral experiment, the rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (30 mg/kg), placed supine on the rat board, blood was collected from the abdominal aorta, the animal was decapitated, and the hippocampus was isolated, homogenized, centrifuged, and the supernatant obtained. The expression levels of IL-1β, IL-6 and TNF-α in rat serum and the hippocampus were detected by ELISA according to the manufacturer's protocol (Multisciences, Hangzhou, Zhejiang, China). The absorption was measured at the wavelength of 450 nm.

Quantitative real-time PCR (qRT-PCR)

Total RNA in the hippocampus was extracted with Trizol reagent (Servicebio, Wuhan, Hubei, China). RNA concentration and purity were detected using a Nanodrop 2000 spectrophotometer. 1 μg RNA was reverse transcribed into cDNA according to the manufacturer's protocol (Servicebio, Wuhan, Hubei, China). The obtained cDNA was used as the template in qRT-PCR according to the instructions. The primer sequences were as follows:

GAPDH: F: CTGGAGAAACCTGCCAAGTATG; R: GGTGGAAGAATGGGAGTTGCT; Raf1: F: TGTTTGATGGCTCCAGTTGC; R: AGCGTGCTTTCTTACCTTTGTG; MEK2: F: TGAATGAGCCACCTCCCAAG; R: ATAGCCAGCCAGCGAAGTCC; ERK1/2: F: TTCAGGACCTCATGGAGACGG; R: GCCACATACTCGGTCAGAAAGC; NF-κB: F: GGGACTATGACTTGAATGCGG; R: CAGCCAGGTCCCGTGAAATA.

Western blot

Total protein in the hippocampus was extracted for Western blot detection. The protein samples were mixed with RAF-1, MEK-2, ERK1/2, NF-κB, and β-actin as an internal reference (all obtained from Servicebio, Wuhan, Hubei, China).

Immunohistochemistry

The paraffin sections were deparaffinized for antigen retrieval, washed three times with phosphate buffer saline (PBS), 5 min each time, and then serum-blocked and then added to primary antibody RAF-1 (1:200), primary antibody MEK-2 (1:200), primary antibody ERK1/2 (1:200), primary antibody NF-κB (1:200), and incubated overnight at 4 °C. The sections were washed 3 times with PBS, 5 min each time, diluted secondary antibody (1:1000) was added, incubated at room temperature for 50 min, washed 3 times with PBS, 5 min each time, DAB color developing solution (Servicebio, Wuhan, Hubei, China) was added dropwise, hematoxylin was used as the counterstain and returned to blue, then dehydrated and made transparent. After drying, the sections were mounted and observed under the microscope.

Statistical analysis

SPSS 24.0 software was used for statistical analysis of the experimental data, measurement data were expressed as mean ± SD, and the *t*-test (comparison between two groups) or LSD analysis of variance was used when normal distribution and homogeneity of variance were satisfied. For comparisons between multiple groups, the Dunnett's-T3 test was used to compare uneven variance, and $P < 0.05$ was considered statistically significant.

RESULTS

Acupuncture at Back-Shu point improved the general state and prolonged sleep time in rats

PCPA was injected intraperitoneally in rats to construct an insomnia model. Compared with the Con group, the sleep latency of rats in the Model group was prolonged and the sleep time was shortened, indicating that the insomnia rat model was successfully established (Figure 1). PCPA can cause general status and behavioral changes in rats[13]. Rats in the Model group showed a poor mental state, fighting and biting each other, with reduced food intake, increased drinking water, dull and damp hair, and poor hair glossiness. After acupuncture treatment, aggressive behavior in rats decreased, food intake increased, and water intake decreased (Table 1). Compared with rats in the Model group, the sleep latency of the Acupuncture group and the U0126 group was shortened and the sleep time was prolonged (Figure 1). In conclusion, acupuncture at Back-Shu acupoints improved cognitive behavioral changes and emotional disturbances caused by insomnia.

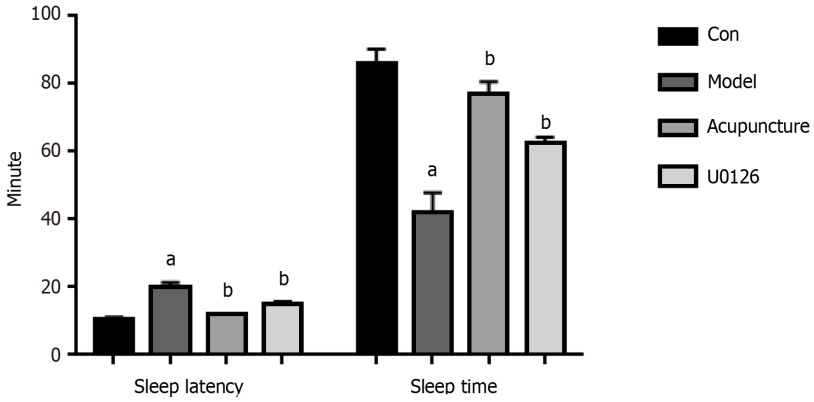
Effects of acupuncture at Back-Shu point on the behavior of insomnia rats

We carried out location experiments to evaluate the memory ability of rats. With the increase in training times, the average escape latency of rats in each group gradually shortened, showing that rats with increased training, remembered the platform. However, the trend in average escape latency in rats was basically the same. After treatment, compared with the Con group, the escape latency of the Model group was prolonged. Compared with the Model group, the escape latency of rats in the Acupuncture group and U0126 group was shortened (Figure 2A). The spatial exploration experiment was used to evaluate the spatial memory ability of rats. The movement trajectories of rats in the Model group showed that the movement trajectories of rats in the four quadrants were basically the same. In contrast, the trajectories of rats in the Con group and the Acupuncture group were primarily concentrated in quadrant III (Figure 2B). Compared with the Con group, the time taken to cross the original platform and the quadrants of the original platform were significantly reduced in the Model group. Compared with the Model group, the number of large crossings of the original platform and the quadrant of the original platform increased in the Acupuncture group and the U0126 group (Figure 2C). These results indicated that acupuncture treatment improved the learning and memory ability of rats and promoted

Table 1 General state of the rats (*n* = 10)

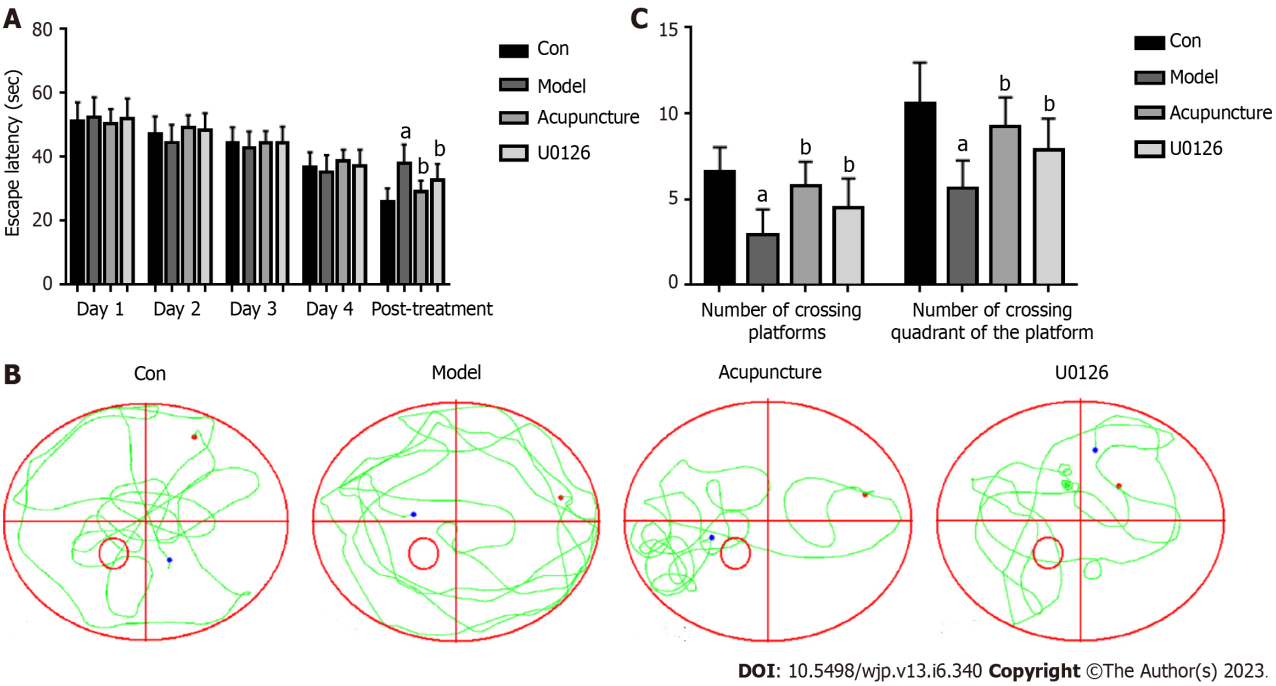
Group	Dietary volume	Drinking volume	Mental state	Hair glossiness	Aggressive behavior	Sensitivity
Con						
Model	- - -	+ + +	- - -	- - -	+ + +	- - -
Acupuncture	-	+	-	- -	+	-
U0126	- -	+ +	-	- -	+	-

-: Represents the degree of reduction; +: Indicates the degree of increase.



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Figure 1 Effects of acupuncture at Back-Shu point on sleep latency and sleep duration in rats. $^{a}P < 0.05$, compared to the Con group; $^{b}P < 0.05$, compared to the Model group.



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Figure 2 Effects of acupuncture at back-shu point on the behavior of rats. A: Average escape latency of rats; B: Spatial exploration movement trajectories of rats; C: Spatial exploration results of rats. $^{a}P < 0.05$, compared to the Con group; $^{b}P < 0.05$, compared to the Model group.

the recovery of learning and memory function.

Acupuncture at Back-Shu point increased inflammation in insomnia rats

Inflammatory cytokines act as mediating signals between the sleep-wake cycle and the immune system. Abnormal secretion of inflammatory cytokines can cause sleep-wake cycle disorder and lead to insomnia. As shown in Figure 3A-C, compared with the Con group, the secretion of inflammatory cytokines (IL-1β, IL-6 and TNF-α) in serum of the Model group was decreased. After acupuncture and U0126 treatment, the secretion of IL-1β, IL-6, and TNF-α in the serum of rats were significantly increased. In the rat hippocampus, we found the same trend in inflammatory cytokine secretion (Figure 3D-F).

Acupuncture at Back-Shu point inhibited the ERK/NF-κB signaling pathway

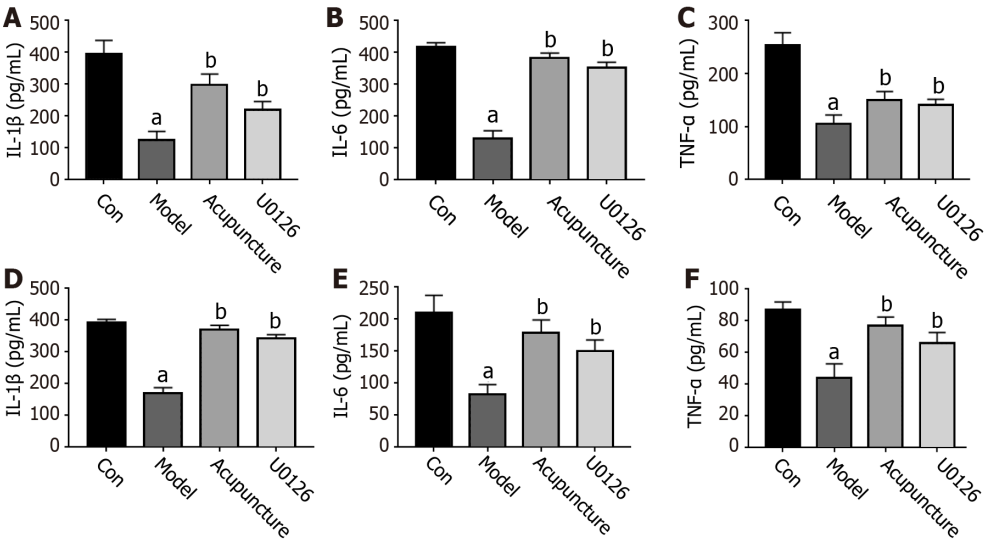
The ERK/NF-κB signaling pathway is closely related to the body's immune system. It plays an important role in the synaptic plasticity of neurons in brain regions, which mainly regulates learning and memory processes. U0126 is a highly potent inhibitor of ERK1/2, MEK-1, and MEK-2. The qRT-PCR results showed that compared with the Con group, the mRNA expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in the hippocampus of the Model group were increased. In addition, acupuncture and U0126 significantly inhibited the expression of these genes (Figure 4). The protein expression levels of the ERK/NF-κB signaling pathway related genes were detected by Western blot and immunohistochemistry, and the results were consistent with the trend in mRNA expression (Figure 5). In conclusion, we believe that acupuncture at Back-Shu point can improve insomnia in rats by inhibiting the ERK/NF-κB signaling pathway.

DISCUSSION

Insomnia is a common disease that not only reduces patients' life quality, but also causes other physical diseases, significantly impacting patients' lives[14]. Due to their reproductive ability, easy feeding, easy modeling and experimental operation, and similar sleep-wake cycle and biological regulatory function to humans, rats were selected to construct the insomnia model in this study. PCPA can inhibit sleep and affect the expression of serotonin (5-HT). As an inhibitor of tryptophan hydroxylase, an essential enzyme in the process of 5-HT biosynthesis, PCPA can reduce the concentration of 5-HT in the brain and serum by inhibiting it, thus causing disorder of the sleep-wake cycle[15]. After intraperitoneal injection of PCPA in rats for three consecutive days, the rats showed circadian rhythm disorder, frequent daytime activity, wet and dark hair, increased aggression during stimulation, and mutual fighting and biting behaviors, which lasted for one week, which was consistent with the clinical symptoms caused by insomnia, indicating that the insomnia model was successfully established.

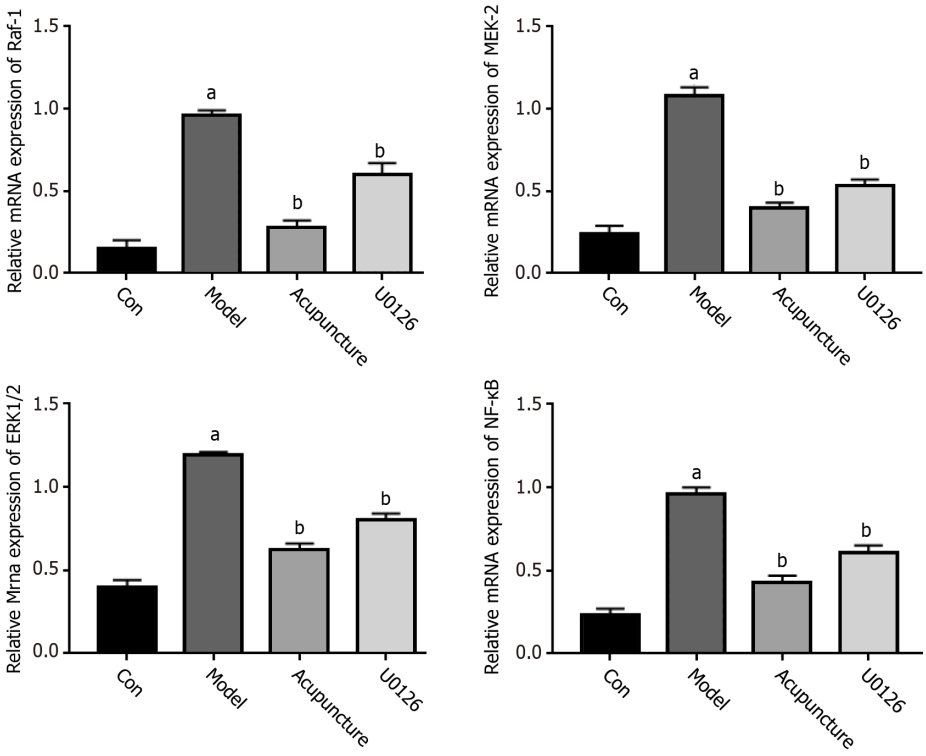
In traditional Chinese medicine, insomnia belongs to the category of "sleepless" and the Back-Shu point is the acupoint on the bladder meridian, which is closely related to the brain. Currently, the five acupoints most commonly used in treating insomnia by acupuncture at Back-Shu point are Xin Yu, Gan Yu, PI Yu, Fei Yu, and Shen Yu[16]. This study found that continuous application of acupuncture at Back-Shu point for seven days can promote appetite, prolong sleep time and improve the mental state, activity, and excessive behavior. The results of the Morris water maze test showed that compared with the Model group, the ability of positioning navigation and space exploration of rats in the Acupuncture group and U0126 group improved to varying degrees, the latency in seeking platform escape was shortened, and the number of swims across the platform was increased. In conclusion, the results show that acupuncture at the Back-Shu point can improve the cognitive behavior changes and emotional disorders caused by insomnia, improve learning and memory ability in rats, and promote learning and memory function recovery.

The sleep-wake cycle is bidirectional in the immune system. Activation of the immune system will change the sleep state, which can lead to increased sleep duration, and lead to the occurrence of insomnia[17]. Cytokines in the sleep-wake cycle and immune system mediate between signals, and through the receptor act on the peripheral nervous system or the central nervous system neurons, astrocytes and microglia, through afferent nerve fibers and blood to the brain signals, cause inflammation and then insomnia[18]. In recent years, the role of inflammatory cytokines in maintaining the NREM sleep cycle has been extensively studied in animal experiments. Anti-inflammatory factors (IL-4, IL-10) can reduce the duration of NREM sleep, and proinflammatory factors (1L-1β, IL-2, IL-6, TNF-α) can promote the duration and depth of NREM sleep[19-21]. The results of the present study showed that compared with the Con group, the proinflammatory cytokines, IL-6, 1L-1β and TNF-α in the Model group rats' serum and hippocampus were significantly decreased ($P < 0.01$), suggesting that insomnia can result in a proinflammatory cytokine secretion imbalance, affect the body's immune system, resulting in sleep cycle disorder, consistent with previous research results. Compared with the Model group, the secretion of IL-1β, IL-6 and TNF-α in the Acupuncture group and U0126 group were significantly increased, suggesting that acupuncture at Back-Shu point may participate in the regulation of sleep and the immune system, improve the secretion of proinflammatory cytokines, maintain the balance of cytokines, and promote recovery of the body's immune system and the improvement of insomnia.



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Figure 3 Acupuncture at Back-Shu point increased secretion of inflammatory cytokines in rats. A-C: Secretion of IL-1β, IL-6 and TNF-α in serum; D-F: Secretion of IL-1β, IL-6 and TNF-α in rat hippocampus. [a]*P* < 0.05, compared to the Con group; [b]*P* < 0.05, compared to the Model group.



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Figure 4 Relative mRNA expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in rat hippocampus. [a]*P* < 0.05, compared to the Con group; [b]*P* < 0.05, compared to the Model group.

The MAPK signaling family is divided into the ERK, JNK, ERK5/BMK1 and P38 MAPK signaling pathways, of which the ERK-mediated MAPK signaling pathway is considered a classical MAPK signal transduction pathway[22]. The ERK signaling pathway transfers extracellular signals into cells through the RAF-MEK-ERK cascade effect and then regulates the expression of downstream key target NF-κB, which affects the occurrence of diseases. RAF-1, MEK-2, ERK1/2 and NF-κB are essential targets in the RAF-MEK-ERK-NF-κB pathway, which regulate cell proliferation, apoptosis, differentiation and other physiological activities, and participate in the pathogenesis and clinical symptoms of insomnia[23-25]. This study showed that compared with the Con group, the mRNA and protein expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in the hippocampus of the Model group were significantly increased ($P < 0.01$), and the number of positive cells increased, suggesting that the pathogenesis of insomnia may

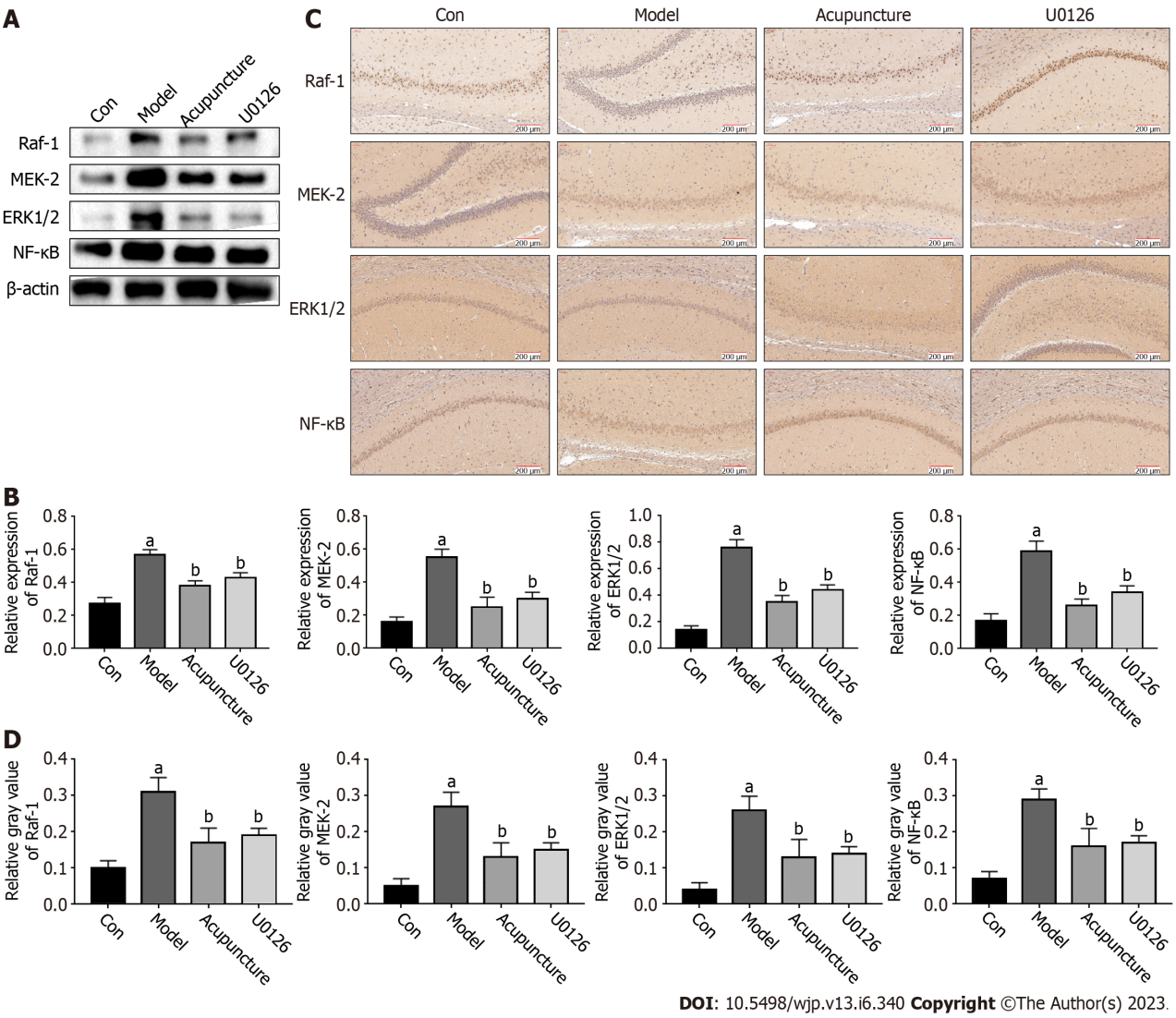


Figure 5 Acupuncture at Back-Shu point inhibited the ERK/NF-κB signaling pathway in rats. A: The expression of ERK/NF-κB pathway-related proteins in rat hippocampus was detected by western blot; B: The relative protein expression level of RAF-1, MEK-2, ERK1/2 and NF-κB in rat hippocampus; C: The expression levels of ERK/NF-κB pathway-related proteins in the hippocampus in rats were detected by immunohistochemistry, scale bars = 100 μm (× 200); D: The gray values of RAF-1, MEK-2, ERK1/2 and NF-κB. $^{a}P < 0.05$, compared to the Con group; $^{b}P < 0.05$, compared to the Model group.

be related to activation of the ERK/NF-κB pathway. To further investigate whether acupuncture at the Back-Shu point improves insomnia by inhibiting the ERK/NF-κB signaling pathway, U0126 was injected into the tail vein of rats. U0126, a highly efficient pathway inhibitor that selects ERK1/2, MEK-1, MEK-2 and other families, can simultaneously inhibit ERK and MEK through a non-competitive pathway, have an impact on the RAF-MEK-ERK cascade reaction, further inhibit cell apoptosis, migration, invasion, and regulate the expression of related proteins[25,26]. Studies have shown that U0126 can effectively inhibit the proliferation, migration and apoptosis of cancer cells *in vivo*, and antioxidant protection of neuronal cells; thus, it is widely used in the treatment of nerve damage, sleep disorders, decreased learning and memory ability, and cancer caused by hypoxia and ischemia[27-29]. Compared with the Model group, the mRNA and protein expression levels of RAF-1, MEK-2, ERK1/2 and NF-κB in the Acupuncture group and U0126 group were significantly down-regulated ($P < 0.01$), suggesting that acupuncture at Back-Shu point and injection of U0126 inhibited activation of the ERK/NF-κB signaling pathway.

CONCLUSION

In summary, acupuncture at Back-Shu point can promote appetite, prolong sleep time, improve learning and memory ability, maintain the balance of proinflammatory cytokine secretion, and improve rats' mental state, activity, and excessive behavior. We believe that the pathogenesis of insomnia may be related to activation of the ERK/NF-κB signaling pathway. Acupuncture at Back-Shu point may inhibit

conduction of the ERK/NF-κB signaling pathway, down-regulate the mRNA and protein expression of RAF-1, MEK-2, ERK1/2 and NF-κB in the pathway, increase the secretion levels of proinflammatory cytokines IL-1β, IL-6 and TNF-α, maintain the balance of cytokines, and protect nerve cells. Thus, acupuncture may promote the body's immune system recovery and play a role in the treatment of insomnia.

ARTICLE HIGHLIGHTS

Research background

The characteristics of insomnia are dissatisfaction with sleep, including difficulty beginning or maintaining sleep, waking up with/or early morning, accompanied by related daytime damage, such as fatigue and emotional disorders. Western medicine mainly uses sedatives and hypnotic drugs to treat insomnia, and long-term use is prone to drug resistance and other adverse reactions. Acupuncture has a good curative effect and unique advantages in the treatment of insomnia.

Research motivation

To explore the molecular mechanism of acupuncture at Back-Shu point for insomnia.

Research objectives

To provides a new insight into the treatment of insomnia by acupuncture at Back-Shu point from the perspective of traditional Chinese medicine.

Research methods

We first prepared a rat model of insomnia, and then carried out acupuncture for 7 consecutive days to explored the effect of acupuncture. The Morris water maze test was used to assess behavioral change. The detailed mechanism research was detected by RT-qPCR, ELISA, and Western blot.

Research results

Some Western drugs can improve insomnia symptoms, but their high drug dependence and adverse reactions limit their clinical application. Our study provides new insights into the treatment of insomnia symptoms from the perspective of traditional Chinese medicine. Our study fills a gap in the treatment of insomnia with acupuncture at Back-Shu point and provides a new treatment for insomnia.

Research conclusions

This study suggest that acupuncture at the Back-Shu point can improve the insomnia by inhibiting the ERK/NF-κB signaling pathway and increasing the release of inflammatory cytokines in the hippocampus. Acupuncture at the Back-Shu point has promoted the treatment of insomnia and benefited the public's sleep health.

Research perspectives

This paper provides new ideas for the treatment of insomnia from the perspective of acupuncture.

FOOTNOTES

Author contributions: Zhang MM and Zhao JW contributed equally to this work; Gao XY, Zhang MM and Zhao JW designed the study; Zhang MM, Zhao JW, and Li ZQ conducted the study; Zhang MM and Shao J contributed new reagents and analytical tools; Zhang MM analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

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Psychological impact of cancer scale: Turkish validity and reliability study

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Abstract

BACKGROUND

In the diagnosis and treatment of cancer, it is important to evaluate the components of psychological adjustment. Considering the key role of nurses in providing care to patients, it is important to evaluate patients, to determine high-risk patients and to use tools with acceptable validity and reliability to develop care plans.

AIM

To analyze the Turkish validity and reliability of The Psychological Impact of Cancer Scale (PICS).

METHODS

This methodological study was conducted with 257 cancer patients admitted to the oncology-haematology clinic and outpatient clinic of a University Hospital between February and October 2021. After the translation process of the scale, content and construct validity were conducted. Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) was examined with construct validity, while item analyses and internal consistency analysis were conducted for reliability.

RESULTS

Analyses and assessment results showed that the content validity index of the scale was 0.96. In the exploratory factor analysis of the Turkish adaptation study, total variance rate explained was found as 84.98%. Factor loads of all items were between 0.82 and 0.94. It was found that Cronbach Alpha values were between

0.860 and 0.930 and total scale Cronbach Alpha value was 0.844. EFA and CFA showed that Turkish form of 12-item and 4-factor. The Psychological Impact of Cancer Scale was confirmed with no changes to the original scale. CFA revealed good fit indices.

CONCLUSION
Turkish PICS is a valid and reliable measurement tool for the evaluation of individual's psychological response to cancer diagnosis and treatment and for being used in clinical practice.

Key Words: Cancer; Patient; Psychological impact; Reliability; Validity

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Core Tip: In the diagnosis and treatment of cancer, it is important to evaluate the components of psychological adjustment. Considering the key role of nurses in providing care to patients, it is important to evaluate patients, to determine high-risk patients and to use tools with acceptable validity and reliability to develop care plans. A valid and reliable intercultural adaptation of Turkish the Psychological Impact of Cancer Scale can be useful in making comparisons across settings and to be used in the psychological assessment of cancer in Turkish patients. Therefore, the aim of this study is to conduct validity and reliability of Turkish version of the scale. In this research, it was seen that the Turkish version of the 12-item and 4 sub-dimensional Cancer Psychological Impact Scale was confirmed without any change in the original scale form.

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INTRODUCTION

Cancer is the second leading cause of death globally and it was evaluated as the cause of one in six deaths in 2020[1]. Cancer continues to grow globally by causing a huge physical, emotional and financial burden on individuals, families, societies and health systems. Survival rates in many cancer types continue to increase with early diagnosis, good treatment and quality care[1,2]. Cancer patients develop emotional, psychological and behavioural reactions before diagnosis, during diagnosis, during treatment, after treatment, during disease progression and during terminal / palliative periods. Due to the unexpected and difficult to control nature of cancer, it is known that the diagnosis and treatment process is disturbing and traumatic for the individual[3]. With this aspect, cancer, which can be associated with metaphors such as "war", "the angel of death", "winter" and "monster' by patients, may cause radical changes in the lives of individuals[4]. During the treatment phase, treatment methods such as examinations and surgery, chemotherapy and radiotherapy come to the fore according to the type of cancer[5]. It may cause a decrease in the quality of life during the treatment phase by disrupting many issues such as social life, activity, work life, sexual life, *etc*.[6-8]. These changes related to the process and treatment of cancer represent an important stress factor for any patient and create both physical and psychological threats to the patient[9,10]. Compared with the general population, studies have shown patients with malignancies to have higher rates of distress, anxiety and depression[11,12].

"The Psychological Impact of Cancer Scale (PICS)" which was developed by Hulbert-Williams *et al* [13] in 2019 for the evaluation of the components of psychological adjustment to cancer diagnosis and treatment is one of the measurement instruments with high validity and reliability. It is an easily applicable 12-item scale with which the psychological impact of cancer on patients can be evaluated [13]. Considering the key role of nurses in providing care to patients, it is important to use tools with acceptable validity and reliability to evaluate patients, to determine patients with high risk and to develop care plans[8]. A valid and reliable intercultural adaptation of Turkish the Psychological Impact of Cancer Scale can be useful in making comparisons across settings and to be used in the psychological assessment of cancer in Turkish patients. At the same time, the scale can be easily applied to cancer patients since it has a small number of items. The scale is expected to be useful in terms of evaluating the psychological impact of cancer on Turkish patients and will make it easier to decide whether patients need psychological support. For this purpose, the aim of the study is to conduct validity and reliability of Turkish version of the scale.

MATERIALS AND METHODS

Study design and sample

This methodological study was carried out at Oncology-Haematology clinic and outpatient clinic of a University between February and October 2021. Population of the study consisted of cancer patients receiving treatment between these dates. The sample included 257 volunteering patients who met the research criteria (having been diagnosed with cancer at least for 3 mo, being older than 18 years of age, not having any psychiatric problems and being able to communicate sufficiently) between the aforementioned dates. In scale adaptation studies, at least 5 individuals for each item should be reached for factor analysis. If it is not a problem to reach the sample, 10 individuals for each item should be reached. The Psychological Impact of Cancer Scale consists of a total of 12 items. Aiming to reach at least 10 cancer patients for each item, the study was completed with 257 patients[14].

Outcome Measurements

Personal Information Form: This form prepared by the researchers includes 9 questions to find out patients' socio-demographic and disease-related characteristics (age, gender, marital status, educational status, employment status, duration of disease, stage of disease, presence of another chronic disease and type of treatment).

PICS: It was developed by Hulbert-Williams *et al*[13] in 2019 to evaluate the psychological impact of the disease in cancer patients. 12-item PICS is used to evaluate the components of psychological compliance with cancer diagnosis and treatment. Each item is answered with "Totally suitable (1)", "Not suitable (2)", "Suitable (3)", "Totally suitable (4)". The scale is a 4-likert type scale. It consists of 4 factors: Cognitive distress (2, 6, 7); Cognitive avoidance (8, 10, 11); Emotional Distress (3, 5, 12); Spiritual Coping (1, 4, 9). Factor scores are calculated by adding the scores obtained from items in each scale. There are no reversely coded items[13].

Data Assessment: Study data were analysed with IBM SPSS (Statistical Package for Social Sciences) 22 and Scientific Software International, Inc. LISREL 8.8. In data analysis, number and percentage were used for evaluation of personal information. Content and construct validity were analysed with expert views, Barlett Tests, Kaiser-Meyer-Olkin Index (KMO), exploratory factor analysis (EFA), confirmatory factor analysis (CFA) and principle components analysis. In terms of reliability, internal consistency was determined with Cronbach's a coefficient, Pearson correlation analysis, item-total score correlation, composite reliability coefficient (CR) and average variance explained (AVE).

Ethical Considerations: Fırat University Non-Interventional Research Ethics Committee (2020/12 numbered) approved the study. Official permission was taken through e-mail from the researcher who developed the scale for adapting the scale into Turkish and using the scale in the study. Helsinki Declaration of Human Rights was adhered to while carrying out the study. Verbal consent was taken from study participants after the aim of the study was explained.

Stages in the adaptation of the scale to Turkish: Official permission was first obtained from the author *via* e-mail to adapt and use PICS in Turkish. Adaptation phase of the scale was carried out in five steps. Language validity was carried out in the first step; two linguists translated the scale into Turkish independently. Translation was followed with a form including the expressions in scale items, which was examined by two Turkish language experts. These experts examined whether scale items were suitable, checked Turkish language validity and cultural appropriateness and made corrections. Following the corrections, scale items were collected in a single form and they were back translated into the original language by a language expert[14]. Turkish form was found to be similar to the English form after the original scale and the translated form were compared.

In the second step, content validity was performed to prove both language and cultural equivalence and content validity of items with numerical values[15]. Content Validity Index (CVI) of the items was calculated with percentage of agreement between the opinions of at least 3 and at most 20 experts[16]. A pilot study was conducted in the third step. In scale adaptation studies, with the pilot study, a sample of about 30 should be reached, the scale should have an internal consistency value of ≥ 0.70 and it should be checked whether item total correlation is lower than 0.30[15]. In the present study, the pilot study was conducted with 30 cancer patients. With the pilot study, it was determined that the questions were understandable. The data of the pilot study were not included in study data. After the pilot study, the study was initiated without making any corrections in the light of this information. In the fourth step, EFA and CFA were conducted for construct validity[14,17]. Acceptable range of CFA goodness of fit values were found as $5 > \chi^2/df < 2$, RMSEA < 0.08, RMR < 0.08, SMR < 0.08, NFI > 0.80, CFI > 0.90, IFI > 0.90, GFI > 0.90, AGFI > 0.85, PGFI > 0.50, and PNFI > 0.50[14,18-20]. In the fifth step, to determine the reliability of the scale, test-retest reliability with an interval of two weeks in data collection stage, Cronbach alpha reliability coefficient Pearson Correlation analysis, item-total score correlation, composite reliability coefficient and mean explained variance were used[21-24].

RESULTS

Mean age of the patients was found as 59.32 ± 12.89 in the study. It was found that 51.4% of the patients were female, 53.7% were primary education graduates, 91.1% were married, 47.9% had a disease duration between 1-5 years, 40.5% were in stage 2, 86.4% were not employed, 67.3% were receiving only chemotherapy and 65.8% did not have another chronic disease.

Results on validity

Exploratory factor analysis: KMO value was 0.799 and χ^2 value was calculated as 2310.444 as a result of Barlett' s Test of Sphericity analysis in the study. Test results were found to be significant at $P = 0.000$ Level of significance (Table 1). The sample size was found to be adequate and suitable for factor analysis and this showed that the analysis could be continued[14,20].

In the exploratory factor analysis, it was found that the scale explained 84.98% of total variance (Table 2). Due to the number of factors in the EFA, Varimax factor rotation method was applied and the scale items were checked in terms of items with cross-loading. The factors with an eigenvalue of > 1 were evaluated while determining the factors. It was found that the scale items were grouped under 4 factors with factor load values found as > 0.30 (0.82-0.94). Varimax rotation method results showed that. It was found that there were no items that had to be deleted from the scale[14,25]. The values obtained showed that the scale consisted of 12 items and 4 factors.

CFA: In Table 3, CFA fit index values were found as: $\chi^2 = 116.49$, df = 47 ($P < 0.05$), $\chi^2/df = 2.47$, RMSEA = 0.076, CFI = 0.97, NFI = 0.95, IFI = 0.97, RMR = 0.034, SRMR = 0.059, GFI= 0.92, AGFI= 0.88, PGFI= 0.56 and PNFI = 0.68. It was found that model fit was acceptable and some values showed perfect fit[14, 18-20]. Figure 1 shows PATH diagram obtained with CFA.

In the study, it was found as a result of EFA and CFA that Turkish form of 12-item and 4-factor "PICS" was confirmed without any changes to the original scale form. All these results obtained show that the scale has high validity in Turkish culture.

Results regarding reliability

For reliability analysis, the data were reapplied two weeks later to 50 individuals from the sample on whom EFA was conducted. Test retest correlation coefficient was found as 0.923 for the whole scale, as .0951 for "Cognitive avoidance (F1)" factor, as 0.992 for "Cognitive distress (F2)" factor, as 0.904 for "Spiritual coping (F3)" factor and as 0.993 for "Emotional distress (F4)" factor (Table 4).

Cronbach Alpha coefficient was calculated to find out the internal reliability of the scale. It was found as 0.930 for "Cognitive avoidance" factor, as 0.0914 for "Cognitive distress" factor, as 0.899 for "Spiritual coping" factor and as 0.860 for "Emotional distress" factor. Total Cronbach Alpha coefficient was found as 0.844 (Table 4).

In this study, AVE value was found as 0.89 and CR value was 0.96 for cognitive avoidance factor; AVE value was 0.78 and CR value was 0.91 for cognitive distress factor; AVE value was 0.77 and CR value was 0.91 for spiritual coping factor, and AVE value was found as 0.67 and CR value was found as 0.86 for emotional distress factor. As a result, it was found that all CR values were higher than AVE values and AVE values were found to be higher than 0.50, which is the critical value (Table 4). When the item-total correlation coefficients of the scale were examined, it was found that all item total correlation coefficients were higher than 0.30 (0.41-0.63) (Table 2).

DISCUSSION

Content validity

Opinions of 5 experts were taken for content validity. CVI was used to evaluate expert opinions. The fact that CVI value was > 0.80 shows that there is agreement between expert opinions[26,27]. In the evaluation after expert opinions, CVI value was calculated as 0.96 in this study. This result shows that there is agreement among experts and the scale measures the subject sufficiently and content validity is met.

Construct validity

KMO and Bartlett's Sphericity test evaluated the appropriateness and sufficiency of the data for factor analysis. It is stated in literature that Bartlett's Sphericity test should be statistically significant and KMO value should be at least 0.60 for factor analysis[28]. In this study, Bartlett's Sphericity test value is 2310.444 and it is statistically significant ($P = 0.000$). KMO value was calculated as 0.799. These results show that data base and sample size are suitable for factor analysis[28]. The data base and sample size in this study are similar to those of Hulbert-Williams *et al*[13] who developed the original scale.

In order to determine the number of factors, eigenvalue was taken as ≥ 1 and it was found that the scale consisted of four factors (cognitive distress, cognitive avoidance, emotional distress, spiritual coping)[29,30]. The original scale also consists of four factors[13]. In the exploratory factor analysis, it

Table 1 Results of the Kaiser–Meyer–Olkin measure of sampling adequacy and Bartlett's test of Sphericity

Tests		Test results	
KMO		0.799	
Bartlett Sphericity Test	χ^2	2310.44	$P < 0.001$
	SD	66	
	P value	0	

Table 2 Exploratory factor analysis results of Psychological Impact of Cancer Scale

Scale items	Communality	Corrected item-total correlations	Cronbach's alpha if item deleted	Factor load values			
				F1	F2	F3	F4
Item 8	0.909	0.411	0.839	0.943			
Item 10	0.894	0.492	0.834	0.917			
Item 11	0.848	0.454	0.837	0.888			
Item 2	0.887	0.511	0.7		0.833		
Item 6	0.87	0.538	0.7		0.83		
Item 7	0.879	0.556	0.7		0.829		
Item 1	0.887	0.46	0.68			0.837	
Item 4	0.836	0.635	0.67			0.827	
Item 9	0.882	0.536	0.5			0.831	
Item 3	0.798	0.543	0.67				0.83
Item 5	0.764	0.51	0.66				0.833
Item 12	0.812	0.54	0.66				0.831
Eigenvalue	-	-	-	2.686	2.587	2.52	2.406
Total explained variance (%) = 84.98%	-	-	-	22.382	21.555	21.001	20.051

was found that the 4-factor scale explained 84.98% of the total variance. In multi-factor scales, explained variance is desired to be over 40% and the higher total variance, the stronger the construct validity is[29,30]. In this study, high explained variance shows that construct validity is robust. It was decided in which factors the scale factors would be included by examining the factor loads. Factor load should be ≥ 0.30[25]. In this study, it was found that the factor loads of the items in the scale were between 0.82 and 0.94 and factor loads were very high. In this study, the fact that factor loads obtained from each scale were > 0.30 shows that the scale has a robust factor structure.

It is reported in literature that CFA should examine the construct revealed with exploratory factor analysis[31]. In this study, it was found with EFA that the scale has 4 factors, as in the original scale. For 4-factor CFA, factor loads of all factors were > 0.30 and goodness of fit indices were (GFI, NFI, CFI and IFI) > 0.90, RMSEA = 0.076. χ^2 value divided by degree of freedom was χ^2/df =2.47. A robust and significant correlation was found between the scale and factors. In literature, a model fit indicator of > 0.90, $\chi^2/df < 5$ and a RMSEA value of < 0.08 are considered as good fit indicators[14,18-20]. CFA results of the present study are in parallel with the criteria reported in literature. In their study, Hulbert-Williams *et al*[13] calculated RMESA value as 0.083. CFA results show that the data are consistent with the model, the four factor construct is confirmed, factors are associated with the scale and the items in each factor define their own factor sufficiently. In this study, EFA and CFA results supported construct validity and showed that the scale is a valid tool.

Reliability analysis

Cronbach's alpha coefficient shows whether the scale items measure the same characteristics and whether the items are correlated with the subject to be measured. Cronbach's alpha value is expected to be as close to 1 as possible. Cronbach's alpha coefficients between 0.60 and 0.80 show that the scale is reliable, while those between 0.80 and 1.00 show that the scale is highly reliable[23,29,32]. In this study, both total and factor α values of the scale are > 0.90. These results show that PICS Turkish version is a reliable measurement tool in evaluating the psychological reactions of patients towards cancer. Hulbert-

Table 3 Confirmatory factor analysis results

Fit criteria	Found	Appropriate	Acceptable	Result
χ^2/df	2.47	< 2	< 5	Perfect fit
RMSEA	0.076	< 0.05	< 0.08	Acceptable fit
CFI	0.97	> 0.95	> 0.90	Perfect fit
NFI	0.95	> 0.95	> 0.80	Acceptable fit
IFI	0.97	> 0.95	> 0.90	Perfect fit
RMR	0.034	< 0.05	< 0.08	Perfect fit
SRMR	0.059	< 0.05	< 0.08	Acceptable fit
GFI	0.92	> 0.95	> 0.90	Acceptable fit
AGFI	0.88	> 0.95	> 0.85	Acceptable fit
PGFI	0.56	> 0.89	> 0.50	Acceptable fit
PNFI	0.68	> 0.89	> 0.50	Acceptable fit

CFI: Comparative fit index; RMSEA: Root mean square error of approximation; RMR: Root mean square residual; NFI: Normed fit index; IFI: Incremental fit index; SRMR: Standardized root mean square residual; GFI: Goodness of fit index; AGFI: Adjusted goodness of fit index; PGFI: Parsimony goodness of fit index; PNFI: Parsimony normed fit index.

Table 4 Correlations between factors, mean scores and reliability results

Factors	α	AVE	CR	mean ± SD	Test-retest (*r*)
F1	0.93	0.89	0.96	2.57 ± 0.66	0.951
F2	0.914	0.78	0.91	2.32 ± 0.85	0.992
F3	0.899	0.77	0.91	2.69 ± 0.71	0.904
F4	0.86	0.67	0.86	2.66 ± 0.80	0.993
PICS total	0.844	-	-	2.56 ± 0.50	0.923

α: Cronbach Alpha Coefficient; *r*: Correlation; AVE: Average variance extracted; CR: Construct Reliability; PICS: Psychological Impact of Cancer Scale.

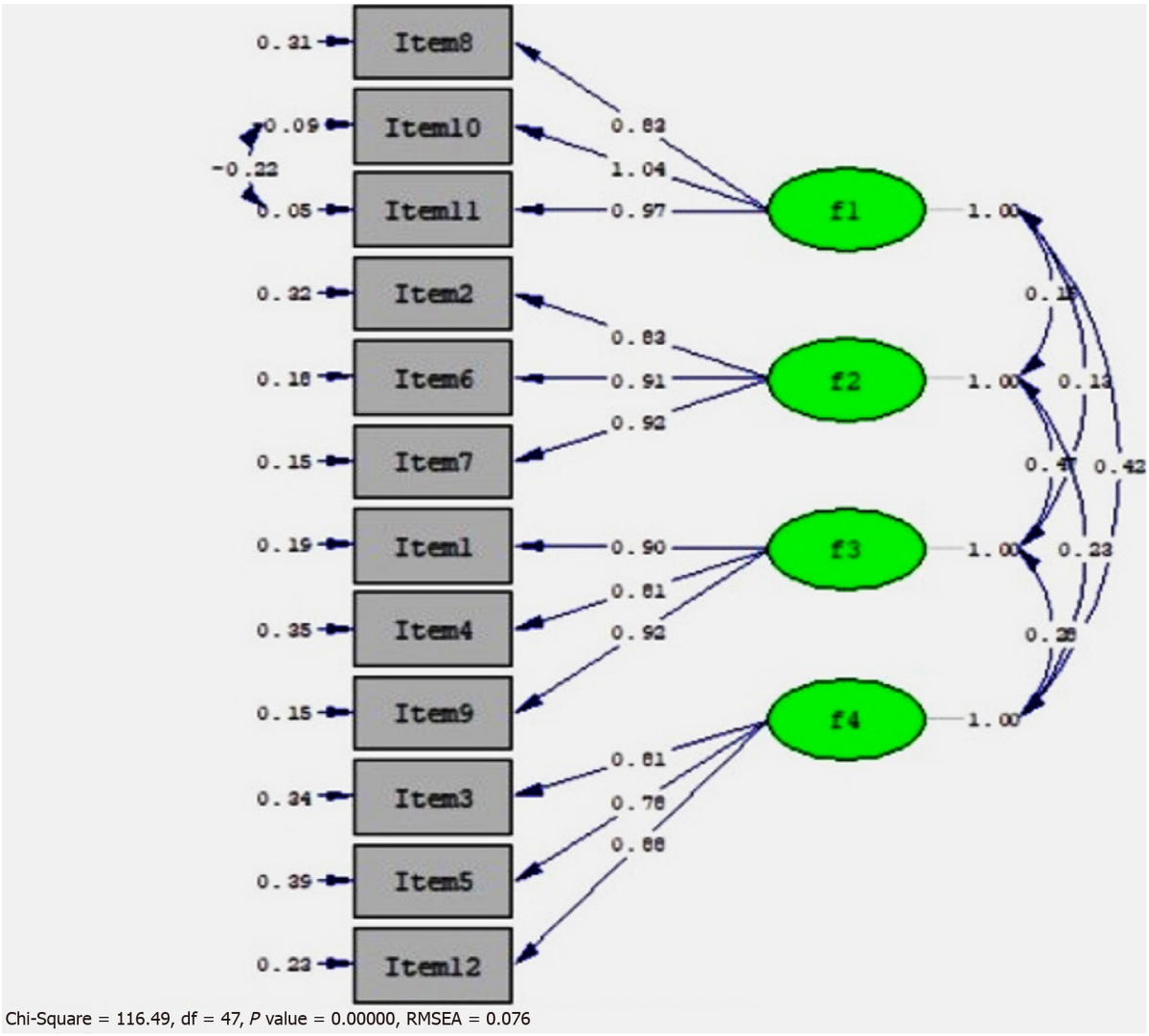
Williams *et al*[13] found the total Cronbach alpha of the scale as > 0,62. In this study, AVE value was 0.89 and CR value was 0.96 for cognitive avoidance factor; AVE value was 0.78 and CR value was 0.91 for cognitive distress factor; AVE value was 0.77 and CR value was 0.91 for spiritual coping factor, and AVE value was 0.67 and CR value was 0.86 for emotional distress factor. The fact that AVE value is > 0.50 and CR value is > 0.80 shows that the scale has good reliability[33]. In addition, values of CR > AVE; AVE > 0.5 are required for convergent validity[24]. As a result, it was found that all CR values were found to be higher than AVE values and AVE values were > 0.50, which is the critical value.

Item-total score analysis is recommended to prove whether the items in the scale measure the variable to be measured. Item-total score analysis explains the correlation between the scores obtained from each item of a scale[34]. In item-total score analysis, it is expected of the correlation to be positive and the correlation value to be > 0.20. When item-total correlation coefficients were examined in the present study, all item total correlation coefficients were found to be > 0.30 (0.41-0.63). Item-total correlation coefficients of the original scale were between 0.33 and 0.73. These results show that the tem-total correlation coefficients in the present study are similar to the original scale and item reliabilities are high.

One of the best ways to measure consistency of scales is test retest method[29,35]. No statistically significant difference was found between the two measurements obtained as a result of test-retest analysis (P > 0.01). Test-reliability coefficients of the scale items were found to be statistically significant in the evaluation of the correlation between first and second application scores of each item (P = 0.000).

Practical implications

The fact that the number of items is low will make implementation and evaluation stages easier. The scale can be easily administered to cancer patients. It is thought that using this scale will be beneficial in terms of evaluating the psychological impact of cancer on Turkish patients and will facilitate deciding



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Figure 1 Path diagram regarding the factor structure of the scale.

on whether patients require psychological support.

CONCLUSION

The present study shows that The Psychological Impact of Cancer Scale is a valid and reliable measurement tool in evaluating the psychological impact of cancer for Turkey sample. The scale can present new research opportunities for researchers who want to work in the field. In terms of researchers, it can be said that the scale is practical and economical since the number of items is low and the expressions are short in the scale.

ARTICLE HIGHLIGHTS

Research background

Cancer patients develop emotional, psychological and behavioural reactions before diagnosis, during diagnosis, during treatment, after treatment, during disease progression and during terminal /palliative periods.

Research motivation

Turkish scale adaptation.

Research objectives
To analyze the Turkish adaptation of The Psychological Impact of Cancer Scale (PICS).

Research methods
This methodological study was conducted with 257 cancer patients.

Research results
Cronbach Alpha value was 0.844. Exploratory factor analysis and Confirmatory factor analysis showed that Turkish form of 12-item and 4-factor.

Research conclusions
PICS Turkish version has acceptable validity. PICS is homogeneous and consistent for Turkish society. Healthcare professionals can use PICS.

Research perspectives
The use of the scale will be useful in evaluating the psychological impact of cancer on Turkish patients.

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FOOTNOTES

Author contributions: Gülcan Bahçecioğlu Turan contributed to the conceptualization, methodology, investigation, original draft, review and editing, supervision; Seda Karaman contributed to the conceptualization, investigation, original draft, review and editing, supervision; Meyreme Aksoy contributed to the conceptualization, investigation, data curation, review and editing.

Institutional review board statement: Fırat University Non-Interventional Research Ethics Committee (2020/12 numbered) approved the study. Official permission was taken through e-mail from the researcher who developed the scale for adapting the scale into Turkish and using the scale in the study. Helsinki Declaration of Human Rights was adhered to while carrying out the study. Verbal consent was taken from study participants after the aim of the study was explained.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There was no commercial involvement in the conduct of this study. Also, none of the authors are members of the editorial board.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author.

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ORIGINAL ARTICLE

Observational Study

Relationship between depression, smartphone addiction, and sleep among Chinese engineering students during the COVID-19 pandemic

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Abstract

BACKGROUND

Existing research has demonstrated that depression is positively related to smartphone addiction, but the role of sleep has not been discussed thoroughly, especially among engineering undergraduates affected by the coronavirus disease 2019 pandemic.

AIM

To evaluate sleep as a mediator of the association between smartphone addiction and depression among engineering undergraduates.

METHODS

Using a multistage stratified random sampling method, a cross-sectional survey was conducted among 692 engineering undergraduates from a top engineering university in China, and data were collected by self-reported electronic questionnaires. The data included demographic characteristics, such as age, gender, the Smartphone Addiction Scale-Short Version (SAS-SV), the 9-item Patient Health Questionnaire, and the Pittsburgh Sleep Quality Index. Pearson correlation and multiple linear regression analyses were used to examine the association between smartphone addiction and depression, while structural equation models were established to evaluate the possible mediating role of sleep.

RESULTS

Based on the cutoffs of the SAS-SV, the rate of smartphone addiction was 63.58 percent, with 56.21 percent for women and 65.68 percent for men, among 692 engineering students. The prevalence of depression among students was 14.16 percent, with 17.65 percent for women, and 13.18 percent for men. Smartphone addiction was positively correlated with depression, and sleep played a significant mediating effect between the two, accounting for 42.22 percent of the total effect. In addition, sleep latency, sleep disturbances, and daytime dysfunction significantly mediated the relationship between depression and smartphone addiction. The mediating effect of sleep latency was 0.014 [$P < 0.01$; 95% confidence interval (CI): 0.006-0.027], the mediating effect of sleep disturbances was 0.022 ($P < 0.01$; 95%CI: 0.011-0.040), and the mediating effect of daytime dysfunction was 0.040 ($P < 0.01$; 95%CI: 0.024-0.059). The influence of sleep latency, sleep disturbances, and daytime dysfunction accounted for 18.42%, 28.95%, and 52.63% of the total mediating effect, respectively.

CONCLUSION

The results of the study suggest that reducing excessive smartphone use and improving sleep quality can help alleviate depression.

Key Words: Smartphone addiction; Depression; Pittsburgh Sleep Quality Index; Engineering students; COVID-19; Mediating effect

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Core Tip: This study described the prevalence of depression and smartphone addiction among engineering students during the coronavirus disease 2019 pandemic and analyzed the relationship between depression, smartphone addiction, and sleep. The results showed that there was an alarmingly high rate of smartphone addiction among engineering students, and they suffered from mild depression on average. Smartphone addiction and poor sleep were significant factors affecting depression, and sleep mediated the relationship between smartphone addiction and depression, including sleep latency, sleep disturbances, and daytime dysfunction.

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INTRODUCTION

The prevalence of depression among college students has aroused broad public concern. A review of studies demonstrated that the pooled prevalence of depressive symptoms was 34%[1]. A recent study of American college students showed that 48.14% experienced moderate to severe levels of depression[2], and the prevalence rate of depression among Chinese college students from 1997 to 2015 reached 23.8% on average[3]. Furthermore, 41.8% of Chinese college students struggled with depressive disorders during the coronavirus disease 2019 (COVID-19) pandemic[4], especially those in places at high risk of COVID-19 spread who showed more severe depressive symptoms[5].

In particular, engineering undergraduates reported higher levels of depression than students in other majors[6]. The heavy academic burden and long study time create tremendous psychological pressure [7]. Previous studies noted that engineering students were under higher pressure than students with nonengineering majors[8,9]. They also had a higher prevalence of depression[10] and suffered from more severe depressive symptoms[8]. Given the importance of engineering education to national development and the adverse mental health of engineering students, it is crucial to identify the influencing factors of engineering students' depression in the context of the COVID-19 pandemic to develop interventions to improve their mental health.

Smartphone addiction is considered a behavioral addiction and refers to an excessive use of smartphones that interferes with users' daily life and has harmful effects[11]. Evidence from China indicated that the prevalence of smartphone addiction among college students ranges from 20% to 50% [12-14]. Notably, smartphone addiction is associated with mental health problems[15]. Smartphone addicts may suffer from social isolation and interpersonal relationship problems[16], musculoskeletal pain and neurological problems[17], emotion dysregulation[18], pressure, and anxiety[19], which may lead to depressive disorders. Previous empirical studies confirmed a positive correlation between

depression and smartphone addiction[20,21], and smartphone addiction exerted a significant effect on depression in different countries and regions[22,23]. However, the mechanism of smartphone addiction's relationship to depression has not been thoroughly discussed, so analyzing the pathway between smartphone addiction and depression is still an important area of study.

Sleep serves as the basis of personal emotional and physical health[24], and empirical studies have verified that poor sleep quality is significantly correlated with depression[25-28]. Some longitudinal studies have indicated that sleep disturbance triggers depression[29]. Lack of sleep makes individuals more sensitive to emotional and stressful stimuli[30], further increasing their risk of depression. According to the gratification theory of the internet, individuals extend their smartphone use time to obtain a sense of satisfaction[31]. Rich smartphone applications also cause addiction in people and make them lose their sense of time[31]. Therefore, problems such as sleep delay, lack of sleep, and poor sleep quality are very likely to occur among college students. Empirical studies have proven that smartphone addiction correlates significantly with poor sleep quality[32,33] and is considered a risk factor for poor sleep quality[34]. The literature in the field also implies that sleep plays a mediating role in smartphone addiction and depression; however, this has not been thoroughly discussed.

There are several research gaps according to the review of relevant studies. First, most of these studies are based on the general population of college students or medical students. More pertinent research needs to be explicitly explored for students of different majors, such as engineering students. Second, college students' mental health status has considerably changed since the outbreak of COVID-19, with a large proportion of students suffering from severe depression and anxiety. Therefore, it is necessary to explore the changes in depression, mobile phone addiction, and sleep status of college students under the influence of COVID-19 and investigate their relationship in this specific context. Third, the role of sleep in the relationship between mobile phone addiction and depression has been poorly analyzed. Although a few studies have confirmed that sleep mediates the relationship between smartphone addiction and depression[35], special attention has been given to engineering students, and the mediating role of sleep needs to be further discussed.

Therefore, this study carried out a cross-sectional survey among engineering students in the context of the COVID-19 pandemic. It adds to the literature mainly by analyzing the relationship between smartphone addiction, sleep, and depression among Chinese engineering students during COVID-19 and investigating the mediating role of sleep in the relationship between smartphone addiction and depression. Based on the extant empirical evidence, the present study hypothesized that there is a significant positive correlation between smartphone addiction and depressive symptoms (Hypothesis I) and that sleep significantly mediates the relationship between smartphone addiction and depression (Hypothesis II). Specifically, engineering students with higher levels of smartphone addiction in the context of the pandemic are more likely to struggle with sleep disorders, which further results in more severe depressive symptoms.

MATERIALS AND METHODS

Participants and procedure

The data were collected from an online survey of 692 engineering undergraduates at a top university in China in December 2021. This study adopted a multistage stratified random sampling method; first, five engineering schools were randomly selected from 25 engineering schools in the university, and then the respondents were randomly chosen according to the size of each school and the number of students in different years. Given the pandemic limiting the face-to-face investigation, the survey team sent electronic questionnaire links to the selected participants' mobile phone numbers or email accounts. All participants were notified of the purpose of the study and gave informed consent to participate. It took approximately 20 min on average to complete the questionnaire, after which students received a cash reward ranging from 8 CYN to 15 CNY. To avoid duplications or fraud in the online survey, the links were exclusive to each student and automatically became invalid after students completed and submitted the questionnaire. Participants were required to complete all questions before submitting the questionnaire. The participants in the study were Chinese engineering undergraduates aged 18-24. The study was reviewed by the ethics committee of Tianjin University and used the STROBE cross-sectional reporting guidelines.

The final sample comprised 153 females (22.11%) and 539 males (77.89%). The age of students ranged from 18 to 24 years old, and the mean age was 20.804 years old (SD = 1.109). Students were distributed evenly from freshmen to seniors, with 76 (10.98%), 242 (34.97%), 231 (33.38%), and 143 (20.67%), respectively. Among them, 608 (87.86%) were of Han nationality, and 84 (12.14%) were ethnic minorities. There were 439 (63.44%) only children and 253 (36.56%) with siblings. In terms of home location, 122 students (17.63%) were from rural areas, and 570 students (82.37%) were from towns. There were 343 (49.57%) students whose fathers completed tertiary education and 349 (50.43%) students whose fathers never received higher education. Regarding the types of high schools, 524 students (75.72%) attended the best local high schools, and 168 (24.28%) attended other high schools.

Measures

Depression: Students' depression was measured using the Patient Health Questionnaire-9 (PHQ-9), a part of the PHQ measuring depressive mood. The PHQ is a 3-page questionnaire self-assessed by patients[36], among which the 9-item depression module is used to measure depressive symptoms. Each item in the PHQ-9 ranges from 0 (no) to 3 (almost every day), and the total score ranges from 0 to 27, with higher scores representing more severe depression[37]. Most studies divide depression scores into five categories based on the severity of depression for practical applications, namely, minimal depressive symptoms (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27), and use a total score of no less than 10 as a reasonable threshold for screening depression[38].

Smartphone addiction: This study used the Smartphone Addiction Scale-Short Version (SAS-SV) to measure participants' smartphone addiction levels. The SAS-SV was adapted by Kwon *et al*[39] based on the SAS. They invited at least 6 experts to select 10 questions from the 33 questions in the SAS and verified that the CVI was greater than 0.78, and the average I-CVI and S-CVI/UA were 0.943 and 0.60. Kwon *et al*[39] verified a Cronbach's alpha correlation coefficient of 0.91 for the SAS-SV in Korea; thus, it was regarded as a suitable tool for assessing smartphone addiction. In this study, experts were invited to translate English SAS-SV questions into Chinese, and appropriate adaptations were made according to the actual situation. For example, in the original item, "constantly checking my smartphone so as not to miss conversations between other people on Twitter or Facebook", "Twitter or Facebook" was changed to "QQ or WeChat" to adapt to the Chinese context. The answers were reported on a 7-point scale, with 1 meaning "strongly disagree" and 7 meaning "strongly agree". The total SAS-SV scale ranges from 10 to 70. Previous studies confirmed that the critical values of male and female smartphone addiction were 31 and 33, respectively[40]. Since the original SAS-SV is a six-point scale with a score range of 10-60, the critical values of male and female smartphone addiction in the study are 36.2 and 38.5, respectively. SAS-SV has been proven reliable and valid in mainland China and Hong Kong. Luk *et al*[40] used the Chinese version of the SAS-SV to measure the smartphone use addiction of adults in Hong Kong and found that the SAS-SV had good internal consistency, with an α coefficient of 0.844. Cheung *et al*[41] tested the SAS-SV scale among Hong Kong children and adolescents, and the α coefficient was 0.86, indicating that the scale had good reliability and validity when applied to Chinese students.

Sleep quality: Sleep quality in the study was measured by the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-assessment questionnaire. It included seven components: Sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The seven components, each scoring 0-3 points, constituted the sleep index, with higher scores denoting worse sleep quality[42].

Statistical analysis

First, descriptive statistical analysis was conducted to demonstrate the general situation of smartphone addiction, overall sleep quality, and depression among engineering students and to compare differences in gender subgroups with the t test. Second, the correlation between smartphone addiction, sleep, and depression was explored with Pearson's correlation analysis. Third, the influence of smartphone addiction on depression among engineering students was examined with multiple linear regression. Depression level was the outcome variable in the regression models, while smartphone addiction level and sleep quality were the core independent variables. It controlled for confounding variables such as students' age, gender, ethnicity, political status, only child status and family socioeconomic status. To identify the effects of different variables, we successively included control variables, smartphone addiction, and sleep in the multiple regression model. Specifically, Model 1, $Y = \beta_0 + \beta_1 x' + \varepsilon$, was developed first to include control variables on engineering students' depression. Mobile phone addiction was further included in Model 2, $Y = \beta_0 + \beta_1 x' + \beta_2 SA + \varepsilon$. The seven sleep index components were then incorporated into Model 3, $Y = \beta_0 + \beta_1 x' + \beta_2 SA + \beta_3 SleepQuality + \beta_4 SleepLatency + \beta_5 SleepDuration + \beta_6 HabitualSleepEfficiency + \beta_7 SleepDisturbances + \beta_8 SleepMedication + \beta_9 DaytimeDysfunction + \varepsilon$. Y denotes the level of depression of engineering students at college. SA represents the degree of smartphone addiction. "x'" represents the control variables, including students' age, gender, ethnicity, political status, only child status, family socioeconomic status, and whether their father received higher education. "ε" defines the error. Finally, a structural equation model was built to examine the mediating role of sleep in the relationship between smartphone addiction and depression. Data analysis was performed by Stata SE 15.

RESULTS

Descriptive statistics and correlations of variables

Table 1 shows the mean and SD of depression, smartphone addiction, and overall sleep quality. The

Table 1 Descriptive statistics of depression, smartphone addiction and sleep (*n* = 692)

Variables	All		Female		Male		Test statistic	*P* value
	Mean	SD	Mean	SD	Mean	SD		
Depression	5.082	4.971	5.425	4.656	4.985	5.056	-0.966	0.335
Smartphone addiction	39.126	11.252	39	10.668	39.161	11.422	0.157	0.876
Pittsburgh Sleep Quality Index	5.496	2.827	5.856	3.023	5.393	2.763	-1.790	**0.074**
Sleep quality	0.990	0.731	1.059	0.771	0.970	0.718	-1.323	0.186
Sleep latency	0.906	0.858	0.928	0.897	0.900	0.848	-0.360	0.719
Sleep duration	1.009	0.766	1.052	0.768	0.996	0.766	-0.797	0.426
Habitual sleep efficiency	0.201	0.542	0.190	0.483	0.204	0.558	0.293	0.770
Sleep disturbances	0.883	0.574	0.915	0.584	0.874	0.571	-0.784	0.434
Sleep medication	0.104	0.441	0.111	0.467	0.102	0.434	-0.224	0.823
Day dysfunction	1.403	1.007	1.601	1.009	1.347	1.000	-2.771	**0.006**

Bold represents statistically significant.

mean score of depression among engineering students was 5.082 (± 4.971); the average score of females was 5.425 (± 4.656), and the average score of males was 4.985 (± 5.056). In general, engineering students experienced mild depression at college, and there was no statistically significant difference in the mean level of depression between female and male students. Regarding the prevalence of depression (Figure 1), 54.91%, 30.92%, 8.82%, 3.61%, and 1.73% of the students exhibited minimal, mild, moderate, moderately severe, and severe depression, respectively. For female students, 82.36% had minimal or mild depression, while 3.92% had moderate or severe depression. For males, 86.83% had minimal or mild depression, whereas 5.76% struggled with moderately severe or severe depression. Given that the extant literature usually uses a PHQ-9 total score of no less than 10 to distinguish whether the participants suffer from depression, 14.16% of students experienced depression disorders (depression ≥ 10), and female and male students who suffered from depressive disorders accounted for 17.65% and 13.18%, respectively (Table 1, Figure 1).

The mean value of mobile phone addiction was 39.126 (± 11.252); the score for females was 39.000 (± 10.668), and the score of males was 39.161 (± 11.422). There was also no significant gender difference in the average mobile phone addiction level. It should be noted that 63.58% of engineering students were addicted to mobile phones, with 56.21% of females and 65.68% of males being addicted to mobile phones. The mean sleep quality score was 5.496 (± 2.827), with female students scoring 5.856 (± 3.023) and males scoring 5.393 (± 2.763). The sleep quality of females was significantly worse than that of males (P = 0.074). Specifically, among the seven components of the sleep quality index, day dysfunction showed a significant gender difference, with girls having higher perceived day dysfunction than boys (P < 0.010).

In sum, smartphone addiction among engineering students was alarming, with more than 60% exhibiting smartphone addiction, which is higher than that reported by most studies in other countries [43-46]. In addition, engineering students suffered from mild depression on average, and female students had more serious sleep problems than males.

The correlation analysis shown in Table 2 demonstrated that depression was positively correlated with mobile phone addiction, with a coefficient of 0.330 (P < 0.01). There was also a positive correlation between depression and PSQI, with a coefficient of 0.503 (P < 0.01). Mobile phone addiction and PSQI were significantly positively correlated with a coefficient of 0.250 (P < 0.01). In addition, depression was positively correlated with the seven components of the sleep index, among which daytime dysfunction had the strongest correlation with a coefficient of 0.414. Mobile phone addiction had a statistically significant positive correlation with sleep quality, sleep latency, sleep disturbances, and daytime dysfunction, among which the strongest correlation was also with daytime dysfunction, with a coefficient of 0.246. The results revealed that depression, smartphone addiction, and sleep index were closely related. The increased risk of smartphone addiction might not only predict the deterioration of sleep quality but also lead to an increase in depressive mood (Table 2).

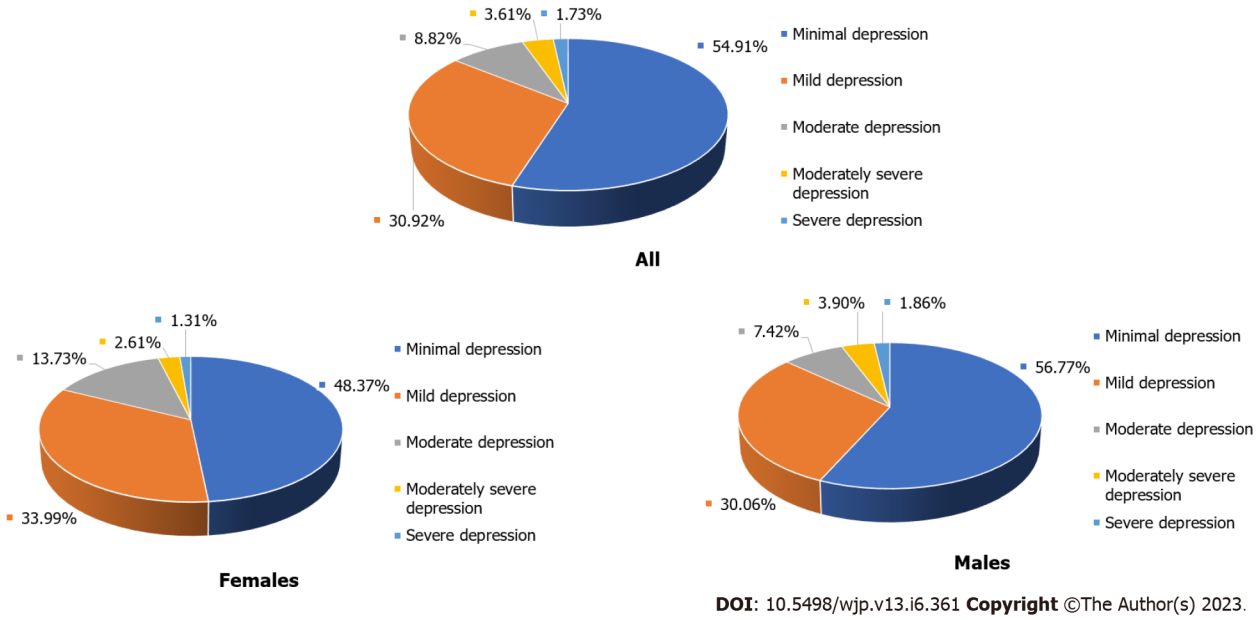
Multivariate regression of depression on smartphone addiction and sleep

The regression model sequentially included the control variables, mobile phone addiction, and sleep index (Table 3). Model 1 shows the influence of engineering students' age, gender, nationality, political status, household registration, and other factors on depression (R^2 = 0.011). Model 2 further displays the

Table 2 Correlation analyses among depression, smartphone addiction, and sleep (*n* = 692)

No.	Variable	1	2	3	4	5	6	7	8	9	10
1	Depression	1.000									
2	Smartphone addiction	0.330[a]	1.000								
3	Pittsburgh Sleep Quality Index	0.503[a]	0.250[a]	1.000							
4	Sleep quality	0.315[a]	0.153[a]	0.738[a]	1.000						
5	Sleep latency	0.334[a]	0.203[a]	0.676[a]	0.483[a]	1.000					
6	Sleep duration	0.164[a]	0.027	0.470[a]	0.204[a]	0.072[c]	1.000				
7	Habitual sleep efficiency	0.090[b]	0.060	0.378[a]	0.151[a]	0.156[a]	0.226[a]	1.000			
8	Sleep disturbances	0.369[a]	0.182[a]	0.539[a]	0.311[a]	0.351[a]	0.091[b]	0.104[a]	1.000		
9	Sleep medication	0.232[a]	0.036	0.373[a]	0.219[a]	0.194[a]	-0.007	0.076[b]	0.191[a]	1.000	
10	Daytime dysfunction	0.414[a]	0.246[a]	0.664[a]	0.425[a]	0.272[a]	0.179[a]	0.016	0.210[a]	0.140[a]	1.000

[a]$P < 0.01$.
[b]$P < 0.05$.
[c]$P < 0.10$.



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Figure 1 Prevalence of depression among engineering students, *n* = 692.

impact of smartphone addiction and control variables on depression ($R^2 = 0.116$). For every one-point increase in the mobile phone addiction score, the average depression score increased significantly by 0.141 among engineering students. Model 3 depicts the influence of the seven components of the sleep index, mobile phone addiction, and control variables ($R^2 = 0.352$). Sleep latency, sleep duration, sleep disturbance, sleep medication, daytime dysfunction, and smartphone addiction significantly affected the depressive mood of students, among which sleep disturbances had the most considerable effect. For every additional point scored by the sleep disturbances, the average depression score of students increased significantly by 1.817. The regression coefficient of smartphone addiction on depression in Model 3 was lower than that in Model 2, indicating that smartphone addiction may indirectly affect depressive mood by affecting sleep quality (Table 3).

Path analysis

This study further established a structural equation model of mobile phone addiction, sleep index, and depression based on correlation and regression analyses to explore possible mediating effects (Figure 2). According to the results in Table 4, the total effect of smartphone addiction on depression was 0.180 ($P <$ 0.01; 95%CI: 0.134-0.233), with the direct effect of smartphone addiction on depression being 0.104 ($P <$

Table 3 Multiple linear regression of depression (*n* = 685)

Variables	Model 1	Model 2	Model 3
Sleep quality	-	-	0.158
Sleep latency	-	-	**0.587**[a]
Sleep duration	-	-	**0.471**[b]
Habitual sleep efficiency	-	-	0.185
Sleep disturbances	-	-	**1.817**[a]
Sleep medication	-	-	**1.436**[a]
Daytime dysfunction	-	-	**1.304**[a]
Smartphone addiction	-	**0.141**[a]	**0.082**[a]
Age	-0.130	-0.113	-0.066
Gender	0.526	0.602	0.112
Nationality	-0.524	-0.570	-0.292
Political status	0.435	-0.035	-0.102
Only child	-0.279	-0.047	0.092
Home location	-0.557	-0.668	-0.392
Family socioeconomic status	-0.170	-0.153	-0.181
Father' education	-0.115	-0.152	0.228
Observations	685	685	685
Adjusted R^2	0.011	0.116	0.352

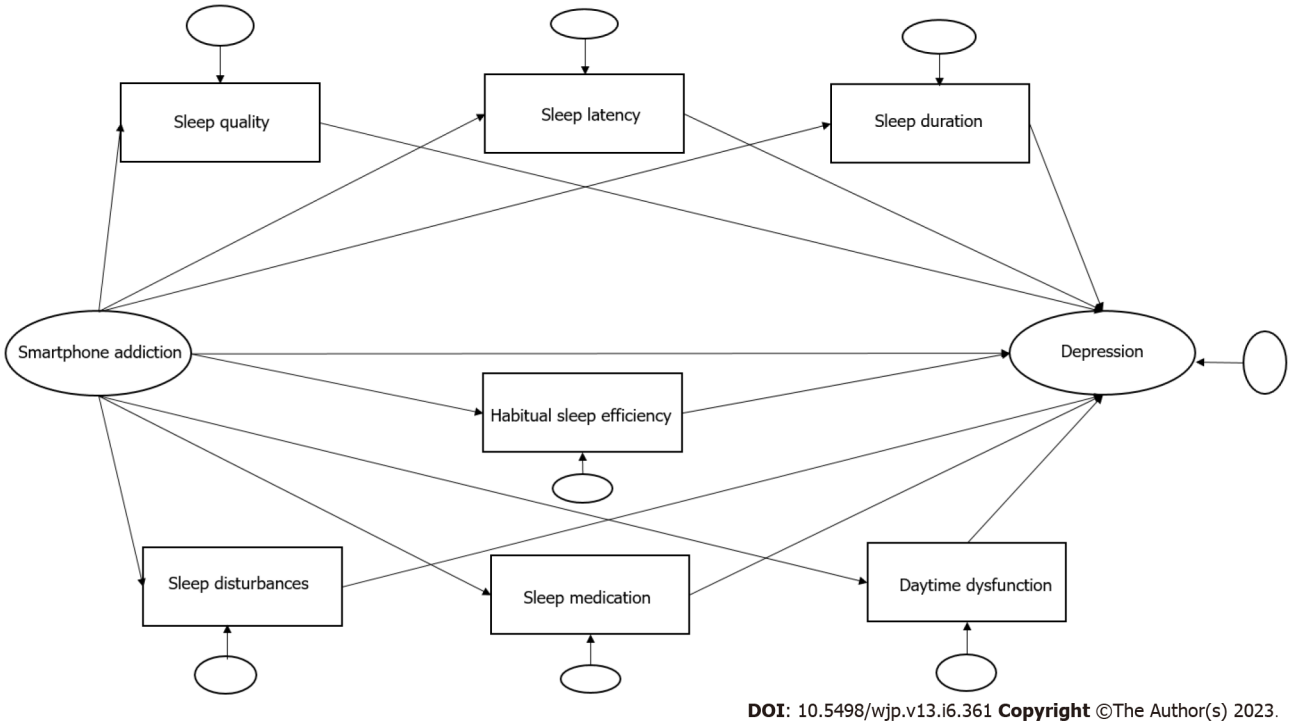
[a]$P < 0.01$.
[b]$P < 0.05$.
[c]$P < 0.10$.
Bold represents statistically significant. Gender: 0 = male, 1 = female. Nationality: 0 = minority nationality, 1 = Han nationality. Political status: 0 = nonparty member, 1 = Communist Party member; only child: 0 = having siblings; 1 = only child. Home location: 0 = rural, 1 = town. Family socioeconomic status: 1 = lower, 2 = lower middle, 3 = middle, 4 = upper middle, 5 = upper. Father's educational level: 0 = never receiving higher education, 1 = completing higher education.

Table 4 Bootstrapping indirect effect and 95% confidence interval for mediation model (*n* = 692)

Effect path	Estimated effect	*P* value	Standard errors	95%CI
Total effects	0.180	**0.001**	0.025	0.134-0.233
Smartphone addiction-depression	0.104	**0.001**	0.022	0.063-0.149
Smartphone addiction-sleep latency/sleep; disturbances/daytime dysfunction-depression	0.076	**0.001**	0.012	0.053-0.102
Smartphone addiction-sleep latency-depression	0.014	**0.001**	0.005	0.006-0.027
Smartphone addiction-sleep disturbances-depression	0.022	**0.000**	0.007	0.011-0.040
Smartphone addiction-daytime dysfunction-depression	0.040	**0.001**	0.009	0.024-0.059

Bold represents statistically significant. 95%CI: 95% confidence interval.

0.01; 95%CI: 0.063-0.149), accounting for 57.78% of the total effect. The mediating effect of sleep on the relationship between mobile phone addiction and depression was 0.076 ($P < 0.01$; 95%CI: 0.053-0.102), accounting for 42.22% of the total. Specifically, the mediating effect of sleep latency was 0.014 ($P < 0.01$; 95%CI: 0.006-0.027), the mediating effect of sleep disturbances was 0.022 ($P < 0.01$; 95%CI: 0.011-0.040), and the mediating effect of daytime dysfunction was 0.040 ($P < 0.01$; 95%CI: 0.024-0.059). The influence of sleep latency, sleep disturbances, and daytime dysfunction accounted for 18.42%, 28.95%, and 52.63% of the total mediating effect, respectively (Figure 2, Table 4).



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Figure 2 Structural equation model of depression, *n* = 692.

DISCUSSION

This study analyzed the relationship between smartphone addiction and depression among engineering students, which has been extensively discussed in the extant literature, yet the underlying mechanisms need to be further explored and verified in diverse contexts and among different populations. The results generally support the hypotheses that smartphone addiction is a significant predictor of depression and that sleep mediates the effect of smartphone addiction on depression. Therefore, alleviating smartphone addiction and improving sleep quality could be an effective strategy to reduce the incidence of depression among engineering students.

The study found a high prevalence rate of smartphone addiction of 63.58% among engineering students in China, with that of male students at 65.68% and female students at 56.21%. The addiction rate appeared to be much higher than in other regions or populations, such as 11.8% in Taiwan[47], 36.8% in Nepal[48], and 41.93% of medical students in Asian countries[49]. There are two reasons for our study's high prevalence of smartphone addiction apart from different cultural backgrounds or various measurement tools. First, given that engineering students usually confront heavy learning tasks and relatively poor face-to-face communication, smartphones might be essential for them to release pressure and maintain social networking. Second, the survey was conducted amid the coronavirus pandemic, which may have exacerbated smartphone addiction among college students. Indeed, the risk of smartphone addiction increased due to the fear of contracting the disease, reduced social interactions due to lockdowns, and long hours of online education. Previous empirical studies confirmed that the smartphone addiction rate of college students in the beginning and fading periods of the pandemic was significantly lower than that in the severe period[50]. It should also be noted that the gender difference in mobile phone addiction in this study was insignificant, inconsistent with existing research findings [24]. This may be due to the small percentage of female engineering students and the widespread influence of online teaching on engineering students.

The prevalence of depression among engineering students in the study was 14.16%, and most students (85.83%) experienced minimal or mild depression during COVID-19. Relevant research found that the prevalence rate of depression among college students was 9.0% in China one month after the outbreak of COVID-19[51] and 34.19% in Spain in March 2020[52]. Forty-four percent of students experienced some depressive thoughts during the COVID-19 pandemic in the United States[53]. The prevalence of depression among engineering students in this study was within the rate range of previous studies, which may be related to the time of the survey. The study was conducted in December 2021, when the pandemic spread was effectively contained, and college students returned to school. The general situation had improved at this stage, and relevant fear and worries had been alleviated, although their study life was still partially affected by the pandemic.

Pearson correlation and multiple regression analysis verified Hypothesis I that smartphone addiction was a significant influencing factor of depression and that high levels of smartphone addiction caused more serious depressive symptoms among engineering students. The result was consistent with most previous studies that there was a positive correlation between mobile phone addiction and depression [21,22,54,55]. The influence of smartphone addiction on depression can be explained by the effect on physiological health and social relations. First, smartphone addiction may result in individuals' unhealthy states, including physical pain, sleep disorders, and inattention, leading to mental health problems such as depression[56]. Second, the overuse of smartphones may increase social isolation and aggravate social anxiety due to the reduction of face-to-face communication and the narrowing of social circles, thus increasing the risk of depression, according to displacement theory and Sullivan's interpersonal theory[57]. The longitudinal study by Herrero *et al*[58] strongly confirmed that smartphone addiction negatively affected college students' social support over time and generated high levels of depression.

For smartphone addiction as a predictor of poor sleep outcomes, the findings agree with most relevant research[59,60]. The overuse of smartphones may expose individuals to blue light from screens for a long time, affecting melatonin levels and thus normal circadian rhythm[61]. Furthermore, when users browse social networking sites through smartphones, the intensity of emotional synchronization may be amplified, resulting in emotional contagion[62]. Smartphone addiction affects the emotions of mobile phone users[35] and increases their psychological pressure[63], thus affecting their normal sleep procedure. In particular, the continuous use of smartphones may lead to bedtime procrastination[31]. The study also found that smartphone addiction was related to sleep quality but not sleep duration, which is consistent with the findings of relevant studies in this field[21,64,65].

Poor sleep positively predicted depressive symptoms in engineering students, especially the components of sleep latency, sleep duration, sleep disturbances, sleep medication, and daytime dysfunction. This finding partially coincides with prior studies[66,67]. Hypothesis II confirms that sleep plays a mediating role in the effect of smartphone addiction on depression, especially sleep latency, sleep disturbances and daytime dysfunction. In fact, poor sleep may affect the emotional regulation ability of the individual through a physiological mechanism[68], and a lack of sleep increases the threat across multiple domains of dysfunction[69]. Sleep is associated with depression at the molecular and neurophysiological levels, and abnormalities in these neurotransmitter systems associated with sleep disorders may contribute to the exacerbation of depression[70]. In addition, sleep disorders affect students' daytime function, resulting in daytime sleepiness, drowsiness, and inattention. This interferes with students' daily tasks and reduces their interest in activities, exposing them to stress and irritability and worsening depressive symptoms[67].

The role of daytime dysfunction was noticeable in both the direct and indirect effects of depression. The influence of daytime dysfunction on depression has been partially confirmed by studies[71,72]. Daytime dysfunction can be regarded as the primary link between night sleep and depression[73]. In fact, daytime dysfunction is closely related to fatigue and burnout[74]. People with high levels of daytime dysfunction tend to be more tired and therefore more vulnerable to depressive moods.

This study suggests that colleges and universities can alleviate depression among students by intervening in smartphone addiction and improving sleep. Studies have discussed effective interventions to reduce smartphone addiction, such as self-awareness and self-control, involuntary restriction, and peer support[75]. College students in adulthood should be soberly aware of the harm of smartphone addiction and seek scientific interventions when necessary. For instance, cognitive behavioral therapy (CBT) was proven effective in a meta-analysis of treatment interventions for adolescents with internet addiction[76]. The group mindfulness-based cognitive-behavioral intervention [77] and mind-body exercise (ME)[78] have been shown to be helpful in the intervention of smartphone addiction among Chinese college students. Thus, cognitive behavioral interventions and MEs (*e.g.*, QigongBaduanjin) should be encouraged. For involuntary restraint, using technology against it, a new mode of intervention for treating smartphone addiction, focuses on monitoring and limiting the use of smartphones with functionalities built into the smartphone and third-party apps. Empirical studies have found that ways to limit notifications and reduce screen time are becoming more widely accepted[79, 80]. Social support, such as favorable peer relationships and harmonious family relationships, is also a protective factor against smartphone addiction[81]. In addition, colleges and universities should also make efforts to expand the accessibility of mental health services to alleviate smartphone addiction.

In addition, physical exercise is the most common way to enhance sleep quality, and sleep therapy training is also practical in improving the sleep situation of college students[82]. For example, sleep training programs for university students with sleep problems proved feasible to significantly enhance students' sleep quality[83]. Psychological interventions such as cognitive behavior therapy for insomnia (CBT-I) have also been recommended to improve sleep[84]. Other interventions, such as improving sleep hygiene, relaxation, mindfulness and hypnotherapy, also play a role in improving sleep quality [85]. Therefore, college students should be encouraged to strengthen their physical exercise, improve their sleeping conditions and restrict mobile phone use to ensure sleep time and quality. For students with serious sleep problems, necessary psychological intervention and medical treatment should be carried out in time to avoid deterioration of the problem and more severe sleep disorders and psychological problems.

The study has several limitations. First, the self-reported data by students may have measurement errors. For example, students may underestimate their smartphone addiction tendency, sleep disorders, and depressive symptoms. Second, other possible influencing factors of depression, such as stress and self-esteem, were not included in this study's analysis framework for assessment. Third, there may exist sample selection bias in the analysis results since written informed consent was obtained before students entered the questionnaire, and those who refused to consent were not included in the sample of this study. Fourth, the cross-sectional data used in this study make it difficult to identify the causal relationship between smartphone addiction and depression. Future studies may investigate the causal relationship between smartphone addiction and depression based on longitudinal data and incorporate more factors into the theoretical mechanisms to discover more effective measures.

CONCLUSION

This cross-sectional study investigated the relationship between smartphone addiction and depression and examined the mediating role of sleep among engineering students in China. First, there was an alarmingly high rate of smartphone addiction among engineering students with no significant gender difference, which has become an urgent issue requiring attention from all parties. In addition, engineering students suffered from mild depression on average, and female students had more severe sleep problems than males. Second, smartphone addiction and sleep deterioration were significant factors affecting depression among engineering students, which might increase the risk of their depressive disorders. Third, sleep latency, sleep disturbances, and daytime dysfunction mediated the relationship between smartphone addiction and depression, among which daytime dysfunction had the most pronounced mediating effect.

The effects of smartphone addiction and sleep on depression may be complicated. Existing literature has confirmed that smartphone addiction could increase the risk of individual depression not only through social reasons (such as social difficulties and task conflicts) but also by affecting physiological functions (such as insomnia and physical pain). In addition, the mediating role of sleep should be considered thoroughly. Sleep disorders can increase the risk of depression by influencing students' emotional control and regulation function or affecting their learning behaviors. Therefore, depression can be alleviated by reducing the use of smartphones and improving sleep quality. Colleges and universities can take measures to relieve depressive problems and improve engineering students' mental health, such as enhancing their self-control ability, restricting mobile phone use, creating a soothing sleep environment, developing a daily routine, and improving physical fitness.

ARTICLE HIGHLIGHTS

Research background

It has been reported that engineering students have severe depressive symptoms, especially during the epidemic. Published research confirms a positive correlation between smartphone addiction and depression. Sleep may play a mediating role in the relationship between smartphone addiction and depression. However, this hypothesis has not been carefully studied in the engineering student population.

Research motivation

Although it is reasonable that sleep plays a mediating role in the relationship between smartphone addiction and depression, this hypothesis has not been discussed in detail. The motivation of this study is to explore the mediating role of sleep in the relationship between smartphone addiction and depression among engineering students.

Research objectives

To investigate whether sleep plays a significant mediating role in the relationship between smartphone addiction and depression among engineering students.

Research methods

During the coronavirus disease 2019 pandemic, we conducted an online survey of 692 engineering students from an engineering university in Beijing, China. The Smartphone Addiction Scale-Short Version was used to assess smartphone addiction. Depression was measured using the 9-item Patient Health Questionnaire. The Pittsburgh Sleep Quality Index was used to measure sleep. We used multivariate regression models and structural equation model analysis to evaluate sleep as a mediator.

Research results

Among 692 engineering students, the rate of smartphone addiction was 63.58%, and the prevalence of depression was 14.16%. According to a multivariate regression model, smartphone addiction and sleep significantly affect depression. Sleep plays a significant mediating role in the relationship between smartphone addiction and depression.

Research conclusions

Current research shows that sleep is a mediator between smartphone addiction and depression. Controlling smartphone use and improving sleep quality can help alleviate depression.

Research perspectives

Future longitudinal studies need to verify the mediating role of sleep in the association between smartphone addiction and depression. In addition, more variables (such as stress and anxiety) need to be controlled for and considered.

FOOTNOTES

Author contributions: Gao WJ and Liu XQ designed the study; Gao WJ and Hu Y undertook the statistical analysis; Hu Y and Ji JL managed the literature searches and analyses; Gao WJ, Hu Y, Ji JL, and Liu XQ wrote the manuscript; and all authors contributed to and have approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Prevalence of posttraumatic stress disorder following acute coronary syndrome and clinical characteristics of patients referred to cardiac rehabilitation

Ivana Sopek Merkaš, Nenad Lakušić, Zdenko Sonicki, Barbara Koret, Sandra Vuk Pisk, Igor Filipčić

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Abstract

BACKGROUND

Studies have demonstrated that patients who have experienced acute coronary syndrome (ACS) have an increased risk of developing posttraumatic stress disorder (PTSD) and experiencing worse survival outcomes than those who do not develop PTSD. Nevertheless, the prevalence rates of PTSD following ACS vary widely across studies, and it is noteworthy that in most cases, the diagnosis of PTSD was based on self-report symptom questionnaires, rather than being established by psychiatrists. Additionally, the individual characteristics of patients who develop PTSD after ACS can differ widely, making it difficult to

identify any consistent patterns or predictors of the disorder.

AIM

To investigate the prevalence of PTSD among a large sample of patients undergoing cardiac rehabilitation (CR) after ACS, as well as their characteristics in comparison to a control group.

METHODS

The participants of this study are patients who have experienced ACS with or without undergoing percutaneous coronary intervention and are enrolled in a 3-wk CR program at the largest CR center in Croatia, the Special Hospital for Medical Rehabilitation Krapinske Toplice. Patient recruitment for the study took place over the course of one year, from January 1, 2022, to December 31, 2022, with a total of 504 participants. The expected average follow-up period for patients included in the study is about 18 mo, and currently ongoing. Using self-assessment questionnaire for PTSD criteria and clinical psychiatric interview, a group of patients with a PTSD diagnosis was identified. From the participants who do not have a PTSD diagnosis, patients who would match those with a PTSD diagnosis in terms of relevant clinical and medical stratification variables and during the same rehabilitation period were selected to enable comparability of the two groups.

RESULTS

A total of 507 patients who were enrolled in the CR program were approached to participate in the study. Three patients declined to participate in the study. The screening PTSD Checklist-Civilian Version questionnaire was completed by 504 patients. Out of the total sample of 504 patients, 74.2% were men (n = 374) and 25.8% were women (n = 130). The mean age of all participants was 56.7 years (55.8 for men and 59.1 for women). Among the 504 participants who completed the screening questionnaire, 80 met the cutoff criteria for the PTSD and qualified for further evaluation (15.9%). All 80 patients agreed to a psychiatric interview. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders criteria. Among the variables analyzed, there was a noticeable difference in the percentage of theoretical maximum achieved on exercise testing between the PTSD and non-PTSD groups. Non-PTSD group achieved a significantly higher percentage of their maximum compared to the PTSD group (P = 0.035).

CONCLUSION

The preliminary results of the study indicate that a significant proportion of patients with PTSD induced by ACS are not receiving adequate treatment. Furthermore, the data suggest that these patients may exhibit reduced physical activity levels, which could be one of the possible underlying mechanisms in observed poor cardiovascular outcomes in this population. Identifying cardiac biomarkers is crucial for identifying patients at risk of developing PTSD and may derive benefits from personalized interventions based on the principles of precision medicine in multidisciplinary CR programs.

Key Words: Cardiac rehabilitation; Acute coronary syndrome; Posttraumatic stress disorder; Psychiatric interview; Multidisciplinary team; Cardiac biomarkers

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Core Tip: The preliminary results of the first large-scale study on a sample of cardiac rehabilitation (CR) patients with posttraumatic stress disorder induced by acute coronary syndrome indicate a significant number of patients who have a persistently increased risk of adverse events, and yet are still insufficiently recognized and treated. The study demonstrates that one possible mechanism of poorer outcomes is the avoidance of physical activity. A multidisciplinary approach involving cardiologists, psychiatrists, and psychologists is required for the identification and early intervention in these patients, and CR and comprehensive social support play a critical role.

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INTRODUCTION

There is evidence to suggest that mental health disorders such as chronic stress, anxiety, and depression are linked to adverse cardiovascular outcomes[1,2]. In particular, stress-related disorders, especially posttraumatic stress disorder (PTSD)[3,4], have been identified as independent risk factors for acute cardiac events[5-7]. There are presumed different interaction mechanisms through which PTSD is associated with cardiovascular diseases. These include psychological (ability to adapt to stress, personality profile, personal traits, social interactions), behavioral (smoking, alcohol, diet, sleep disorders, adherence to prescribed therapy), and biological factors (neuroendocrine dysfunction involving metabolic syndrome, hypothalamic-pituitary-axis dysfunction, inflammation, renin-angiotensin system dysregulation, autonomic nervous system dysfunction)[7-9].

Furthermore, there is a growing recognition of acute coronary syndrome (ACS) as a potential precipitating event for PTSD[10-12], which is now increasingly acknowledged as a medical issue, prompting questions about its prevalence and clinical implications. It has been observed that patients who develop PTSD following an ACS have a higher risk of experiencing recurrent myocardial infarction (MI) and higher mortality rates[5,11,13]. A meta-analysis from 2012 reported a 12% prevalence of significant PTSD symptoms following ACS[11], while a 2021 systematic review found a prevalence range of 3% to 19%[13]. It's worth noting that the higher prevalence rates were observed when PTSD was assessed through self-report questionnaires compared to clinical diagnostic interviews conducted by a psychiatrist who made the diagnosis.

Reports on the characteristics of individuals who develop PTSD after ACS vary greatly, and there is no consensus on the specific demographic or biological risk factors that contribute to its development. In the systematic review from 2021 the authors reported several risk factors for PTSD following MI, including female gender, younger age and prior history of psychiatric disorders[13]. However, the individual characteristics of those who develop PTSD after ACS can differ widely, making it difficult to identify any consistent patterns or predictors of the disorder. Identifying patients at risk for persistent and severe ACS-induced PTSD based on demographic, biological and psychological factors could facilitate the implementation of early preventive measures[14].

While there is a significant correlation between PTSD and acute cardiac events, research on PTSD development following ACS is not as advanced. As a result, mechanisms of interaction are poorly understood. ACS-induced PTSD is associated with an increased risk of recurrence, but this risk is most prominent during the first year after the cardiovascular event, which is much shorter than the time frame required for many of the potential mechanisms linking PTSD to cardiovascular diseases[5]. Early identification and intervention are crucial, especially during this first year, when patients participate in cardiac rehabilitation (CR), which offers a unique opportunity for timely recognition and management of high-risk patients, potentially leading to improved outcomes.

MATERIALS AND METHODS

Study design

This ongoing observational, prospective, analytical case-control study presents preliminary findings on the number of patients who developed PTSD diagnosed by a psychiatrist after an ACS in a sample of patients undergoing CR, and their demographic, behavioral and biological characteristics compared to the control group.

Study subjects

This study enrolled patients who experienced ACS, with or without undergoing percutaneous coronary intervention (PCI), and who were participating in a 3-wk CR program at the at the Special Hospital for Medical Rehabilitation Krapinske Toplice, the largest CR center in Croatia. Patient recruitment for the study spanned a year (from January 1, 2022 to December 31, 2022), and the study ultimately included 504 participants. The expected follow-up period is approximately 18 mo and is currently ongoing. Inclusion criteria: Patients who have completed one month after an ACS (stressful event) before arriving at rehabilitation, both sexes, aged between 18 and 70 years. Exclusion criteria: Patients with a history of cardiac surgery, repeated MI, active psychiatric treatment, diagnosed psychiatric disorder or previously diagnosed PTSD from another cause, active malignancy, clinically unstable patients (acute heart failure, unstable coronary disease, acute infection), and patients who do not wish to participate in the study. Exclusion criteria are also applied to those who develop conditions that are defined as exclusion criteria during data collection, or those who no longer wish to participate in the study.

To identify patients with PTSD, a combination of self-assessment questionnaires and clinical psychiatric interviews were used. The initial screening of patients who agreed to participate in the study involved the use of the PTSD Checklist-Civilian Version (PCL-C) questionnaire[15,16]. For the purposes of this study, the recommended cutoff score for suggesting the possibility of PTSD based on the questionnaire was 30-35 points, given the civilian population. A combination of both scoring methods was employed, using a higher threshold score (35 points) and the requirement of a symptom pattern to

minimize the number of false positives. Participants who met the criteria based on the questionnaire underwent a clinical psychiatric interview, and those who were diagnosed with PTSD in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification[17] by the psychiatrist were included in the group of patients with PTSD (Figure 1).

From the pool of study participants who did not receive a PTSD diagnosis, a subset of individuals was selected for further analysis based on clinically and medically relevant stratification variables such as age, gender, type of ACS [ST-elevation MI (STEMI), non-STEMI (NSTEMI), or unstable angina (UA)], who underwent rehabilitation during the same period. They form a second group of participants that matches the characteristics of those with a PTSD diagnosis, in order to enable comparability of the two groups.

Data collection

The study obtained medical data through a patient's anamnesis, including their age, gender, lifestyle habits such as smoking and alcohol consumption, family history of cardiovascular disease (positive or negative), comorbidities such as hypertension, dyslipidemia, diabetes, and body mass index (BMI). Additionally, diagnostic tests were conducted during the three-week rehabilitation period to obtain data on important biological characteristics [laboratory testing, exercise stress test (ergometry), echocardiogram].

Follow-up

The expected average follow-up period of patients in the study is approximately 18 mo and is currently ongoing. Both groups of patients will be contacted (letter sent by post along with questionnaires and subsequently contacted by phone). They will complete the PCL-C scale again, a questionnaire on quality of life, medication adherence, and report any adverse cardiovascular events. In case it is not possible to contact the patient, data will be obtained from family members or primary care physician. After the end of the study, further analysis of the collected data will follow, and the obtained results and conclusions should direct attention to a subpopulation of patients in terms of precision medicine (identification of specific groups of patients).

Statistical analysis

We used the SPSS 29.0.0.0 statistical software package, setting significance level at $P < 0.05$ (2-tailed). For clarity, we present all data in original units (mean ± SD, ranges). For calculations of differences between groups, the student' t test, χ^2 test, Fisher's exact test and Mann Whitney test were used.

Ethical considerations

The study protocol was approved by the ethics committee of the Special Hospital for Medical Rehabilitation Krapinske Toplice. Data regarding patients were extracted from routine medical and treatment records. Patient identities have not been revealed. Written informed consent was obtained from every patient who agreed to participate in the study. All the methods followed the guidelines of the Declaration of Helsinki for medical research involving human subjects.

RESULTS

A total of 507 patients who were enrolled in the CR program were approached to participate in the study, out of which 3 patients refused to participate. The PCL-C questionnaire was completed by 504 patients. Of these, 74.2% (n = 374) were men and 25.8% (n = 130) were women. The mean age of all participants was 56.7 years (55.8 years for men and 59.1 years for women). Out of the 504 participants, 80 individuals met the cutoff criteria for PTSD on the screening questionnaire and qualified for further evaluation, representing 15.9% of the total sample. All 80 patients agreed to psychiatric interview. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to DSM-5 criteria (Figure 1, Table 1).

From 51 PTSD patients, 32 were male (62.7%) and 19 female (37.3%). The average age of male participants diagnosed with PTSD was 52.8 years (range 42-65), and for female it was 56.5 years (range 42-66). Of these PTSD patients, 39 suffered STEMI (76.5%), 12 NSTEMI (23.5%), and there were no cases of PTSD following UA (Table 2).

Patients' characteristic

This preliminary report of the study presents findings on the investigation of demographic, behavioral, and particularly biological factors, and examines the differences in individual characteristics between PTSD and non-PTSD group (which was formed based on clinically and medically relevant variables such as age, gender, type of ACS), and the results are summarized in the table (Table 3).

Among the variables included, the PTSD group had a significantly lower percentage of maximum exercise capacity achieved compared to the non-PTSD group (P = 0.03). No significant differences were

Table 1 All patients included in the study

General data	Value
Patients	504
Age	56.68 ± 7.82 (27-70)
Male patients	374 (74.21%)
Male patients age	55.85 ± 8.04 (27-70)
Female patients	130 (25.79%)
Female patients age	59.05 ± 6.6 (44-70)
PTSD patients after PCL-C questionnaire	80 (15.87%)
Diagnosed PTSD patients	51 (10.12%)

Data are given as mean ± SD (ranges) or values (percentages). PTSD: Posttraumatic stress disorder; PCL-C: Posttraumatic stress disorder Checklist-Civilian Version.

Table 2 Posttraumatic stress disorder/pairs included in the study

General data	Value
Patients in each group	51
Age	54.16 ± 6.64 (42-66)
Male patients	32 (62.75%)
Male patients age	52.78 ± 6.53 (42-65)
Female patients	19 (37.25%)
Female patients age	56.47 ± 6.32 (42-66)
STEMI	39 (76.47%)
NSTEMI	12 (23.53%)
UA	0 (0.0%)

Data are given as mean ± SD (ranges) or values (percentages). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; UA: Unstable angina.

found in commonly observed comorbidities in cardiology patients such as hypertension, diabetes, dyslipidemia, and BMI.

In the study, there were participants who underwent a second PCI as an elective procedure after an acute event and those who experienced cardiorespiratory arrest and other complications following MI. Within the PTSD group, 7 participants (13.7%) underwent an elective PCI during hospitalization due to MI, while in the non-PTSD group, the number was 12 (23.5%). Acute heart failure was reported as a complication of MI in one male participant from each group. Within the PTSD group, one participant had a complication of surgically treated ventricular septal defect, while in the non-PTSD group, one female participant experienced post-procedural atrial fibrillation that was successfully converted to sinus rhythm using amiodarone. In both groups, two patients experienced cardiac arrest and were successfully resuscitated. Complications occurring during the acute phase of ACS and repeated PCI did not prove to be significant risk factors for developing PTSD.

DISCUSSION

To our knowledge, this is the first study on a large sample of CR patients that investigates the prevalence of PTSD after ACS, characteristics of these patients, and possible factors important for clinicians to recognize such patients in a timely manner. Consistent with prior research, it has been demonstrated that the prevalence of PTSD is lower when diagnosed by a psychiatrist rather than relying solely on self- administrated questionnaires. The results confirm that the diagnosis of PTSD after ACS made by a psychiatrist is approximately 10%, which exceeds the prevalence reported in meta-analysis

Table 3 Characteristics of patients

Variable	PTSD	Non-PTSD	*P* value
BMI	29.09 ± 4.15 (21.9-41.9)	28.58 ± 4.15 (20.5-36.4)	0.5373
Smoking	31 (60.78%)	26 (50.98%)	0.3187
Alcohol use	0 (0.0%)	2 (3.92%)	0.495
Family history of cardiovascular diseases	23 (45.1%)	30 (58.82%)	0.1654
History of hypertension	26 (50.98%)	31 (60.78%)	0.3187
History of dyslipidemia	18 (35.29%)	19 (37.25%)	0.8368
History of diabetes	10 (19.61%)	7 (13.73%)	0.4254
LDL	2.15 ± 0.8 (1.1-4.5)	2.28 ± 0.64 (0.9-3.3)	0.3481
LVEF	53.27 ± 10.81 (25-75)	55.78 ± 9.12 (30-76)	0.2078
LVDd	52.2 ± 10.81 (43-66)	50.78 ± 9.12 (41-68)	0.2462
Theoretical maximum percentage in exercise test	88.55 ± 13.35 (46-114)	94.24 ± 13.58 (44-124)	0.0354
WATT in exercise test	126.96 ± 39 (50-200)	132.65 ± 47.83 (50-225)	0.512
METs in exercise test	6 ± 1.36 (2.8-9.89)	6.3 ± 1.45 (3.5-9.29)	0.2754
MPRH percentage in exercise test	76.76 ± 11.02 (54-103)	79.04 ± 9.76 (54-103)	0.2726
PCI in second act	7 (13.73%)	12 (23.53%)	0.2035
Positive exercise test	4 (7.84%)	4 (7.84%)	-
Acute complications	2 (3.92%)	2 (3.92%)	-
Arrest	2 (3.92%)	2 (3.92%)	-

Data are given as mean ± SD (ranges) or values (percentages). BMI: Body mass index; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; LVDd: Left ventricular diastolic diameter; METs: Metabolic equivalents; MPHR: Maximal predicted heart rate; PCI: Percutaneous coronary intervention.

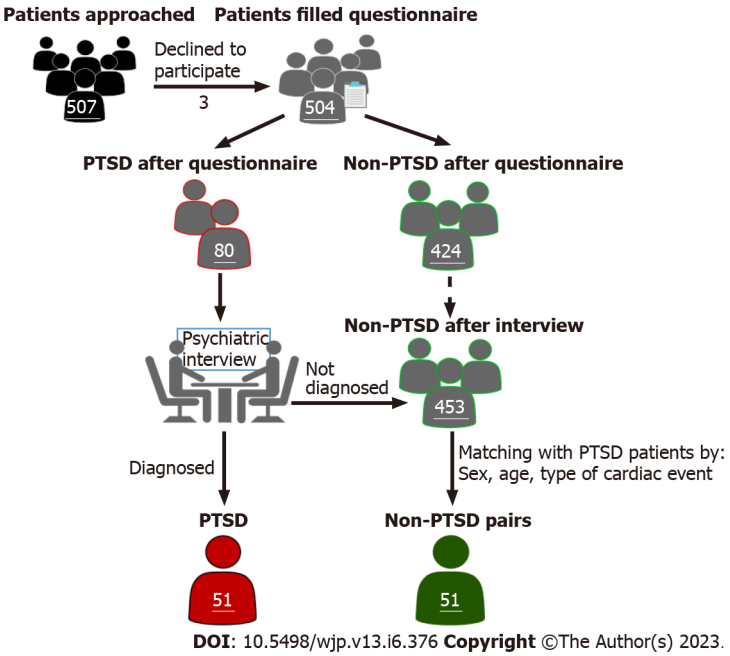


Figure 1 Algorithm for patient selection. PTSD: Posttraumatic stress disorder.

[11] and literature review[13], but similar prevalence has been reported[18]. If only a self-reported questionnaire is used to assess the PTSD symptoms, reported prevalence can be up to 16%. These findings highlight the significant impact of this clinical disorder on a substantial group of patients who

are often underdiagnosed and at increased risk for poor clinical outcomes.

The biological mechanisms in PTSD have been extensively reviewed and could potentially contribute to the modification of cardiac and vascular functions, ultimately leading to the development of cardiovascular events[19,20]. These mechanisms involve a complex set of pro-inflammatory, pro-atherogenic, pro-ischemic, neuro-hormonal, metabolic, and immune reactions. As presented in the table, numerous biological factors were examined regarding the ACS-induced PTSD (Table 3). While no significant differences were found in commonly observed comorbidities (hypertension, diabetes, dyslipidemia, BMI) as well as in left ventricular ejection fraction, the study introduced a novel approach by using results from an exercise stress test which showed a significant difference between the two groups. A standardized protocol is used to measure the maximum amount of oxygen an individual can consume during exercise (VO_2max) and to estimate the maximum watts a patient should attain during the exercise test[21]. The non-PTSP group achieved a significantly higher percentage of their theoretical maximum compared to the PTSP group. Recent research shows that patients with PTSD following ACS may avoid physical activity if they experience cardiac symptoms such as dyspnea and tachycardia, which can be reminiscent of the traumatic event[22]. Our study further confirms that this could be an underlying mechanism that contributes to the negative prognosis of patients with ACS-induced PTSD.

Complications related to ACS, repeated PCI, and even cardiac arrest during the acute phase did not show a significant association with the development of PTSD. However, previous study demonstrated that cardiac arrest-induced posttraumatic symptoms are linked to an increased risk of mortality and cardiovascular disease[23].

A recent meta-analysis provides further support evidence that the presence of PTSD is a risk factor for the subsequent development recurrent cardiac events, such as MI[24]. Due to the significant prevalence of PTSD after ACS, which was confirmed in this study, further research is needed to identify the mediating factors involved in the direct association between PTSD and the subsequent occurrence of adverse cardiovascular events in more precise medical terms.

The latest study highlights the increasing acknowledgement of the importance of social support and the role of CR, emphasizing comprehensive, multidisciplinary approach and early intervention has the potential to exert a favorable effect on the outcomes of these patients[25]. Early psychological assessment and intervention in ACS patients is important, and the inclusion of psychological interventions can improve patients' attendance and adherence to CR programs[26,27]. Therefore, it is essential not to downplay the role of such interventions following ACS. Recent studies suggest that mental health conditions may not be a barrier to CR and that CR may provide an opportunity for greater mental health care and support[28]. Therefore, a CR program with a multidisciplinary team including cardiologists, psychiatrists, and psychologists could be considered as a potential early intervention site, and by combining medical treatment, lifestyle modifications, and psychosocial support, patients may benefit from a more holistic approach to their care, which could lead to improved quality of life, reduced morbidity, and better long-term adherence to lifestyle changes.

Study advantages

The present study is the first large-scale study among rehabilitation patients, excluding patients with a preexisting psychiatric diagnosis (which is not the case in most previous studies, and it is important in explaining pathophysiology) or a history of MI, focusing on a more precise description of PTSD as a secondary risk factor in cardiology patients and revealing possible mechanism of interactions. One of the strengths of the study is also the use of psychiatrist-based diagnosis. By identification of potentially important biomarkers, it may be possible to predict which subgroup of patients is at a higher risk for developing PTSD after an ACS.

Study limitations

This is a preliminary report of an ongoing study, with patients still under follow-up. Some biological markers have not yet been included in the analysis, and comprehensive data analyses will be performed once all data is collected. We do not yet have information on whether all enrolled patients will remain in the follow-up and if we will have complete data for all patients by the end of the study.

CONCLUSION

This study is one of the largest cohorts to investigate the incidence of PTSD after ACS, and it is the first to consider the role of CR in this context, with the diagnosis made by a psychiatrist using the DSM-5 classification system. The preliminary findings of the study reports on substantial group of patients with PTSD induced by ACS (10.1%) and suggest that they may avoid physical activity, which could be one of the underlying mechanisms of the worse cardiovascular outcomes observed in this population. It is imperative to identify potential cardiac biomarkers that could aid in detecting increased cardiac risk in patients with secondary risk factor - ACS-induced PTSD, as current research in this area is limited. Further research is necessary, as there is significant potential value in identifying prognostically useful cardiac biomarkers to predict and prevent the onset of recurrent cardiovascular events and higher

morbidity and mortality rates in this group of patients.

After completing the follow-up period of the present study and conducting complex statistical analyses of all collected data, it may be possible to identify a specific subset of patients who are at risk of developing PTSD and may derive benefits from personalized interventions based on the principles of precision medicine. In this individualized approach, CR with a multidisciplinary team and the development of specific therapeutic and rehabilitation strategies can play a key role in improving quality of life and reducing overall mortality of this vulnerable and previously under-recognized subgroup of patients.

ARTICLE HIGHLIGHTS

Research background

Acute coronary syndrome (ACS) can be a stressor in the development of posttraumatic stress disorder (PTSD). Patients with PTSD after ACS have worse survival outcomes, and studies report different prevalence rates of PTSD following ACS. It is challenging to identify these patients and prevent their unfavorable outcomes.

Research motivation

Clinicians and cardiologists who deal with cardiac rehabilitation (CR) are increasingly noticing patients with elements of PTSD after ACS. The problem is their poorer outcomes, and CR with a multidisciplinary team (cardiologist, psychiatrist, psychologist) can be a place for early detection and intervention in these patients.

Research objectives

In this study we aim to investigate the prevalence of PTSD after ACS in patients undergoing CR and their demographic, behavioral, and biological characteristics. Identifying patients at risk for persistent and severe ACS-induced PTSD based on these characteristics could facilitate the implementation of early preventive measures.

Research methods

This is an ongoing prospective analytical case-control study. The study includes patients who have experienced ACS and are enrolled in a 3-wk CR program. A group of patients with PTSD diagnosis was identified using self-assessment questionnaires for PTSD criteria and clinical psychiatric interviews, and a control group was formed based on clinically relevant variables to enable comparison of these patient groups. Medical data were collected, and diagnostic tests were conducted to obtain data on important biological characteristics [laboratory testing, exercise test (ergometry), echocardiogram]. The expected average follow-up period for patients included in the study is approximately 18 mo.

Research results

Of 504 patients completed PTSD Checklist-Civilian Version questionnaire and 80 (15.9%) met the cutoff criteria for the PTSD and qualified for further evaluation by psychiatrists. Among them, 51 patients (10.1%) were diagnosed with clinical PTSD by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders criteria. Among the variables analyzed, there was a noticeable difference in the percentage of theoretical maximum achieved on exercise testing between the PTSD and non-PTSD groups. Non-PTSD group achieved a significantly higher percentage of their maximum compared to the PTSD group (P = 0.035).

Research conclusions

This study found a significant proportion of patients with PTSD induced by ACS (10.1%), and these patients are under-recognized and not appropriately treated. The study also found that patients with PTSD achieved a lower theoretical maximum on exercise testing, suggesting that they may avoid physical activity, which could be one of the underlying mechanisms for the worse cardiovascular outcomes observed in this subpopulation of patients.

Research perspectives

Early identification of patients with ACS-induced PTSD and intervention are crucial, and CR provides a unique opportunity for timely recognition and management of high-risk patients, potently leading to improved outcomes. Future research could focus on identifying possible cardiac biomarkers to detect patients at risk of developing PTSD after ACS and apply personalized interventions based on the principle of precision medicine. Multidisciplinary CR programs may be particularly effective in addressing the complex needs of patients with ACS induced PTSD.

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FOOTNOTES

Author contributions: Sopek Merkaš I conducted research and wrote first version of the manuscript; Lakušić N and Sonicki Z designed the study and corrected the manuscript; Sonicki Z is involved in analytical tools; Koret B and Vuk Pisk S diagnosed PTSD, contributed in literature review and data processing; Lakušić N, Sonicki Z, and Filipčić I served as scientific advisors, literature review and participate in making critical revisions related to the important intellectual content.

Institutional review board statement: The study was reviewed and approved by the Ethics Committiee and Institutional Review Board of Special Hospital for Medical Rehabilitation Krapinske Toplice on the date 25.5.2021.

Informed consent statement: Written informed consent was obtained from every patient who agreed to participate in the study.

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ORIGINAL ARTICLE

Observational Study

Abnormal volumetric brain morphometry and cerebral blood flow in adolescents with depression

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Abstract

BACKGROUND

Prior research has demonstrated that the brains of adolescents with depression exhibit distinct structural alterations. However, preliminary studies have documented the pathophysiological changes in certain brain regions, such as the cerebellum, highlighting a need for further research to support the current understanding of this disease.

AIM

To study brain changes in depressed adolescents.

METHODS

This study enrolled 34 adolescents with depression and 34 age-, sex-, and education-level-matched healthy control (HC) individuals. Structural and functional alterations were identified when comparing the brains of these two participant groups through voxel-based morphometry and cerebral blood flow (CBF) analysis, respectively. Associations between identified brain alterations and the severity of depressive symptoms were explored through Pearson correlation analyses.

RESULTS

The cerebellum, superior frontal gyrus, cingulate gyrus, pallidum, middle frontal gyrus, angular gyrus, thalamus, precentral gyrus, inferior temporal gyrus, superior temporal gyrus, inferior frontal gyrus, and supplementary motor areas of adolescents with depression showed an increase in brain volume compared to HC individuals. These patients with depression further presented with a pronounced drop in CBF in the left pallidum (group = 98, and peak t = - 4.4324), together with increased CBF in the right percental gyrus (PerCG) (group = 90, and peak t = 4.5382). In addition, 17-item Hamilton Depression Rating Scale scores were significantly correlated with the increased volume in the opercular portion of the left inferior frontal gyrus (r = - 0.5231, P < 0.01).

CONCLUSION

The right PerCG showed structural and CBF changes, indicating that research on this part of the brain could offer insight into the pathophysiological causes of impaired cognition.

Key Words: Voxel-based morphometry; Cerebral blood flow; Arterial spin labeling; Adolescent; Depression; The right percental gyrus

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Core Tip: In this study, we first combined cerebral blood flow (CBF) and voxel-based morphometry (VBM) to study brain alterations in adolescent depression. We also found that the brain function (CBF) changes were mainly in the left pallidum and right precentral gyrus. Meanwhile, we detected alterations in the cerebellum. Our finding about a wide range of brain structure (VBM) changes in adolescent depression contributes to better treatment and prevention strategies for depression.

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INTRODUCTION

Adolescents suffer from high rates of depression that contribute to adverse outcomes, including academic difficulties, substance abuse, behavioral issues, parental conflict, impaired peer interactions, and suicidality[1-3]. Depression rates are exceptionally high among children in middle school, with an incidence of up to 24.3%[4]. Clinical symptoms of depression include feelings of sadness, hopelessness, cognitive impairments, and reductions in motivation and pleasure. Overcoming depression can be particularly challenging among adolescents, with treatment failing to have any pronounced effect in 30%-50% of cases[5]. Recurrence rates are also very high[6], with most adolescents experiencing relapses multiple times in adulthood[7,8]. Adolescence is also a critical period for brain growth[9], and this disease can have a profound negative impact on such development[10]. Despite this fact, many studies have focused on the mental health of adults rather than exploring outcomes in vulnerable adolescent populations[11,12]. As a result, there is an urgent need for in-depth neurobiological research that investigates the pathophysiology of depression to develop effective treatments that can help free adolescents from the symptoms of this debilitating condition.

The results of imaging studies suggest that adolescents suffering from depression exhibit severe structural changes within their brains[13-15]. However, these reported findings have been inconsistent with some studies documenting the thinning of brain regions[16], whereas others note the thickening of certain areas[17]. These inconsistencies may result from a range of patient-specific confounding factors or pharmacological treatment effects. While cerebellar dysfunction has been documented in many disease states[18], changes in the cerebellum in depression remain overlooked mainly[19]. Recent research supports the cerebellum's function in the processing of emotion and its widely recognized role in the context of motor control[20]. Reductions in the gray matter volume in the cerebellum and anterior cerebellar vermis have been documented among adults with depression[21], and some evidence suggests the ability of cerebellar neurons to regulate depression-like behavioral development actively [22].

Given the poorly understood nature of the pathophysiological basis for depression among adolescents, efforts to detect and clarify morphological alterations associated with functional changes provide an opportunity to define these underlying pathogenic processes better. In a previous publication, we used cerebral blood flow (CBF) to assess Major Depressive Disorder(MDD) in adolescents and reported CBF alterations after treatment[22]. Voxel-based morphometry (VBM) is a

technique that is frequently applied to detect structural changes within the brain[23], allowing for the voxel-by-voxel classification of brain volumes in different regions to enable the systematic, reproducible comparison of regions among multiple individuals more effectively than the traditional region of interest (ROI)-based strategies. VBM can assess anatomical differences throughout the brain with a short execution time[23,24] and is widely used in studies of alterations in depressed brains[25-27]. Still, there are also conflicting and heterogeneous results reported by VBM and magnetic resonance imaging (MRI) whole brain analysis[16,17]. These examples encourage the further development of VBM in MDD investigations. CBF can also be detected noninvasively and quantitatively through arterial spin labeling (ASL), in which arterial blood magnetic labeling is leveraged as an endogenous tracer[28]. Investigations have utilized VBM and voxel-based pathophysiology to analyze MDD[29]. Because structural alterations are usually accompanied by functional abnormalities[30,31], we decided to extend our study approach to incorporate VBM with CBF. The current study's findings are consistent with the high repetitive rate of change obtained so far regarding depression[32-34]. The cerebellum's role in depressive symptoms was confirmed in a recent study[35], and elevated pallidum CBF was also detected in patients with mild traumatic brain injury that may lead to cognitive decline[36]. These repeats suggest a potential association between the changes we detected using VBM combined with CBF and MDD dysfunction. Accordingly, in the present study, VBM and CBF strategies were used to evaluate changes in the brains of adolescents with depression.

Regular examinations of a broader range of brain regions are required to understand the pathophysiology of depression in adolescents properly, and unmedicated young people diagnosed with first-episode depression are the perfect model for studies of disease-related brain alterations. For the present analysis, these patients were thus the primary subjects of interest in hopes of detecting previously unrecognized yet clinically significant abnormalities present in depressed adolescents that have yet to undergo pharmacological treatment. These approaches offer a promising means of exploring the pathophysiology of adolescent depression while also validating and expanding upon previously published results[37].

Through the application of VBM and CBF techniques, a series of complex structural and functional alterations were documented within the brains of adolescent patients with depression compared to a healthy control (HC) population. The cerebellum was expected to undergo alterations because of its crucial involvement in developmental processes, and depression-related structural and functional changes were anticipated to coincide in several brain regions. These were the two primary outcomes that were expected from the present research.

MATERIALS AND METHODS

Participants

From August 2020 to July 2022, adolescents with depression were recruited from the Department of Psychiatry at Chongqing Medical University's First Affiliated Hospital. The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) was used by senior psychiatrists to confirm the diagnosis of depression in all cases, and symptom severity was assessed with the 17-item Hamilton Depression Rating Scale (HAMD-17). Patients eligible for study participation were individuals of Han ethnicity who were right-handed, exhibited a HAMD score ≥ 17, had no history of antidepressant treatment, were experiencing first-episode depression, had no history of psychotropic drug use, and had no history of anesthetic or sedative, or analgesic drug use within 1 mo before the study initiation. Patients were excluded if they had a history of prior mental health conditions, including schizophrenia or bipolar disorder, a history of drug abuse or dependence, exhibited MRI contraindications, or had been diagnosed with organic brain diseases or severe physical ailments.

Participants in the HC trial were selected from age-, gender-, and education-level-matched subjects with no personal history of mental illness or psychosis among first-degree relatives. The same exclusion criteria were applied for both patients with depression and HCs. In total, 34 treatment-naive first-episode adolescent depression patients and 34 HCs from 12-17 years of age were recruited for study participation.

The First Affiliated Hospital of Chongqing Medical University approved this study (NO. 2017-157). The legal guardians of all participants provided written informed consent, and all participants were provided with a comprehensive overview of the details of the study.

General data collection

Sociodemographic data were collected using a questionnaire regarding participant age, sex, and educational status. For the MINI-KID, the parents of eligible study participants were contacted and informed about this study, after which questionnaire and interview responses were obtained electronically. One professional interviewer conducted the interview processing, which was completed in under two days[38].

HAMD-17 surveys were administered by two psychiatrists with similar levels of training to assess symptom severity based on appropriate guidelines. Two examiners blinded to participant details independently performed all subsequent scoring to ensure the absence of subjectivity.

MRI data collection

MRI scanning was performed with a Signa 3.0 Tesla MRI instrument (GE Medical Systems, WI, United States), yielding T1-weighted, T2-weighted, and T2-fluid-attenuated inversion recovery (T2-Flair) imaging sequences. T2-Flair data were used to detect any evidence of potential brain disorders, with patients exhibiting such conditions being eliminated from further study inclusion.

Structural images were acquired with no gap using the following settings: the number of axial slices = 156, time repetition (TR) = 8.4 ms, echo time (TE) = 3.3 ms, flip angle (FA) = 12°, slice thickness = 1.0 mm, the field of view (FOV) = 240 mm × 240 mm, matrix = 240 × 240, and voxel dimension = 1 mm × 1 mm× 1 mm. Parameters used for ASL image acquisition were as follows: NEX 3, TE 9.8 ms, TR 4639 ms, FOV 240 mm × 240 mm, slice thickness 4.0 mm, post label delay time 1525 ms, 3D spiral k-space filling, points 512, arms 8, acquisition scan slices 40. During imaging, participants were directed to remain awake with their eyes closed, and foam padding was employed to restrict head movement.

Image processing

FSL-VBM was used to analyze structural images[39]. After the initial recovery of these images, they were segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid regions, followed by nonlinear registration-based alignment of these images to the Montreal Neurological Institute (MNI) standard space. Native GM images were then re-registered nonlinearly to the resultant averaged images to produce a template specific to the present study. Native GM images were then registered to this template and modified as appropriate based on local contraction or expansion associated with nonlinear spatial transformation. The altered GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (FWHM = 6.9 mm) as per FSL recommendations[39].

ASL images were analyzed following the earlier reported studies[22,28].

Statistical analysis

SPSS 22.0 (IL, United States) was used to analyze all data. Data are reported as means ± SD and were compared between groups with two-way ANOVA, while comparisons between males and females were made using chi-square tests.

Analyses of GM and WM volumes included group-based comparisons of larger and smaller volumes in HC individuals relative to adolescents with depression. These analyses employed grand mean scaling and absolute threshold masking. Voxel-level GM and WM density were compared between these groups with two-sample t-tests using SPM5. Random Gaussian field theory was used to estimate significant differences among groups using a familywise error-corrected alpha of 0.05. Clusters were displayed as statistical parametric maps in standard anatomical space. Participant age, education status, and total intracranial volume were utilized as covariates when conducting two-way ANOVA analyses of smoothed CBF images, with an initial $P < 0.001$ thresholds for cluster-level false discovery rate (FDR) multiple comparison correction ($P < 0.05$). Regions of the brain affected by sex or group interactions for CBF perfusion were then acquired with the xjview software (https://www.alivelearn.net/xjview). Brain areas with interactive effects were selected as ROIs, and the CBF values for these ROIs were extracted using DPABI[40].

Relationships between brain alterations and depressive symptom severity were explored through Pearson correlation analyses with $P < 0.05$ as the significance threshold.

RESULTS

Participant characteristics

Table 1 provides details regarding the characteristics of the study participants. No differences in age, sex, or education level were detected between depressed adolescents and HCs ($P > 0.05$), whereas HAMD-17 scores differed significantly between these groups ($P < 0.001$).

Depression-related changes in VBM

FSL-VBM analyses exploring differences between groups highlighted increases in the volume of several regions of the brain following correction for multiple testing ($P < 0.05$), including the cerebellum, superior frontal gyrus, cingulate gyrus, pallidum, middle frontal gyrus, angular gyrus, thalamus, precentral gyrus, inferior temporal gyrus, superior temporal gyrus, inferior frontal gyrus, and supplementary motor area (Table 2, Figure 1). No regions of the brain exhibited depression-related decreases in brain volume.

Table 1 Participant demographic and clinical characteristics

Item	depressed adolescents (*n* = 34)	healthy controls (*n* = 34)	t/χ^2	*P* value
Gender (F/M)	23/11	23/11	0[a]	1.00
Age (yr)	15.26 ± 0.99	15.68 ± 1.77	- 1.18[b]	0.24
Education (yr)	10.06 ± 1.98	10.44 ± 1.97	- 0.80[b]	0.43
HAMD-17	26.12 ± 4.43	1.03 ± 1.70	30.84[b]	< 0.001

[a]χ^2 test.
[b]Two sample *t*-test.
The values are illustrated as mean ± SD. F: Female; M: Male; HAMD-17: 17-item Hamilton Depression Rating Scale.

Table 2 Whole-brain group statistics for healthy controls and adolescents with depression

Brain sub-region	Peak (MNI)			Number of voxels	*P* value (FWE corrected)
	X	Y	Z		
HCs > depressed adolescents					
Cerebellum_6_L	73	64	56	973	0
Frontal_sup_medial_L	81	16292	101106	925	0.01
Cingulum_mid_R	103	120	67	221	0.02
Pallidum_R	113	-6	49	211	0.02
Cingulum_mid_L	-4	168	92	146	0.04
Frontal_mid_L	67	70	118	113	0.03
Angular_R	119	116	92	88	0.03
Thalamus_L	85	136	102	74	0.03
Precentral_R	151	134	27	57	0.04
Temporal_inf_R	127	142	46	55	0.04
Temporal_Pole_Sup_L	61	130	98	42	0.04
Frontal- Inf_Oper_L	51	66	105	25	0.04
Occipital_Mid_L	63	126	148	24	0.04
Supp_Motor_Area_L	79	88	52	14	0.04
Cerebellum_3_R	101			13	0.04

HCs: Healthy controls; MNI: Montreal Neurological Institute; FWE: Family wise error.

Depression-related changes in CBF

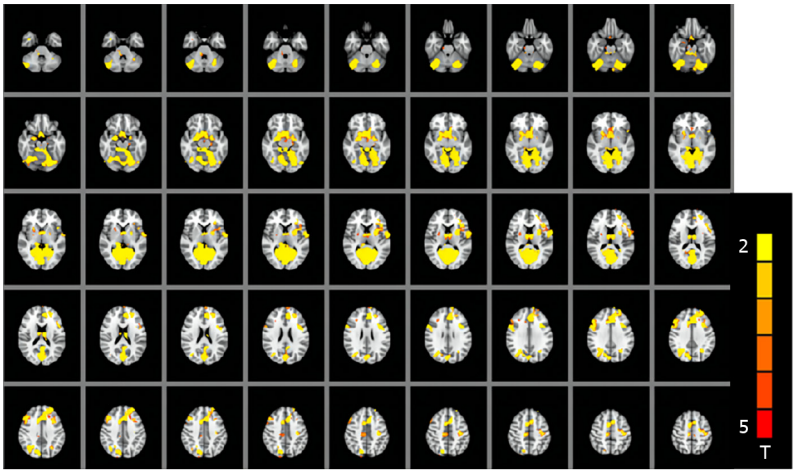
Adolescents with depression exhibited pronounced decreases in CBF in the left pallidum as compared to HCs (group = 98, and peak *t* = -4.4324), together with an increase in the right percental gyrus (PerCG) (group = 90, and peak *t* = 4.5382) (Figure 2). This analysis was performed using a cluster cut-off *P*-value < 0.001.

Correlations between brain alterations and depression severity

In patients with depression, HAMD-17 scores were significantly correlated with the increased volume of the opercular part of the left inferior frontal gyrus (IFG) (r = - 0.5231, *P* < 0.01). No correlations were detected between HAMD-17 scores and other changes in brain volume or CBF (*P* > 0.05).

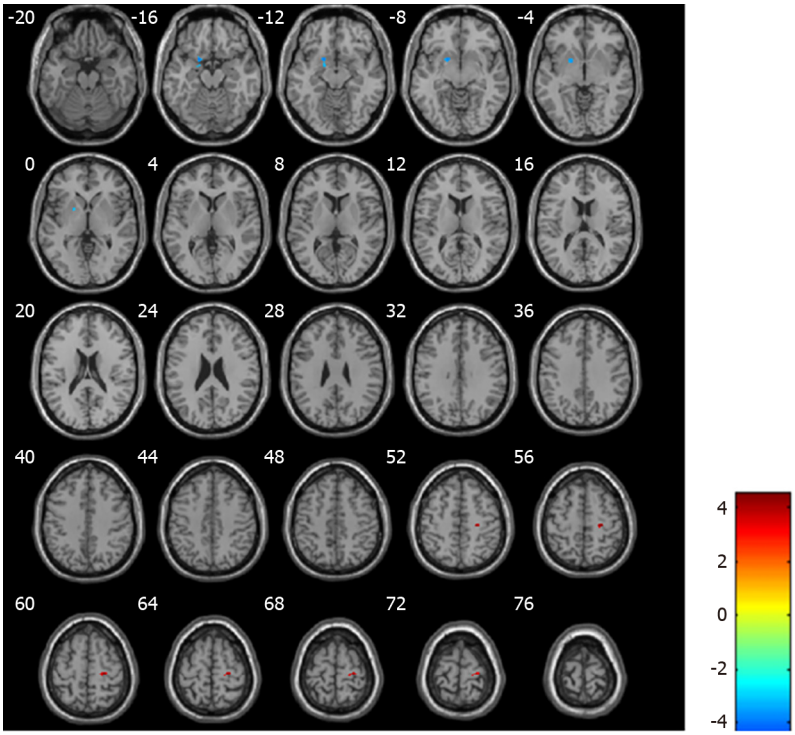
DISCUSSION

The current findings showed that, in contrast to HCs, treatment-naive first-episode depression in adolescents is associated with CBF and brain volume modifications. Notably, increased volume of many



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Figure 1 Two-sample tests comparing healthy controls and adolescents with depression based on a whole-brain mask.



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Figure 2 Differences in cerebral blood flow when comparing healthy controls and adolescents with depression. Blue and red indicate reductions and increases in cerebral blood flow, respectively.

brain regions was observed in adolescent depression patients, with increased CBF in the PerCG and decreased CBF in the left pallidum. HAMD-17 scores in these patients were also negatively correlated with the volume of the opercular portion of the left IFG. In particular, decreases in both volume and CBF were observed in the right PerCG, suggesting that this region may be an important area for future research to understand the pathophysiological bases of depression.

The PreCG regulates primary motor behaviors and has been reported to exhibit alterations in individuals with movement-related disorders, including amyotrophic lateral sclerosis[41] and akinetic-rigid Parkinson's disease[42]. Increased PreCG CBF is correlated with increased reaction time[43], pure apraxia of speech and other forms of impaired verbal fluency[44], and autism[45]. Several studies suggest a relationship between PreCGand emotion[46]. Depression can impair neural plasticity in the motor cortex, contributing to behavioral and cognitive alterations in affected patients[47]. Pathological alterations in the PreCG may thus be functionally linked to depression. An increase in PreCG GM volume has been reported[48,49], with the present results confirming these prior reports and

highlighting a link between these changes and altered CBF.

The left IFG plays a crucial role in the functional and structural brain network that underlies language in neurocognitive models of language perception[50]. The opercular portion of the left IFG is a crucial node connected to multiple cerebellar, cortical, and subcortical structures within the language network [51]. In the present study, adolescents with depression exhibited a correlation between HAMD-17 scores and the volume of this opercular portion of the left IFG, consistent with its potential association with depression severity.

The cerebellum is thought to be closely related to movement, with additional experimental evidence highlighting its association with attention and motor systems[52], as well as with cognition[53]. This link could explain depression-related symptoms, such as cognitive impairment, disinterest, and poor attention. Adolescent depression may affect the cerebellum, contributing to frequent episodes in adulthood. However, it is essential to highlight that the reported increase in the cerebellum in the present study contradicts other published studies in which cerebellar volume was shown to be reduced [54,55]. These differences may be attributable to variations in disease severity, assessment methodology, diagnoses, or treatment approaches.

Other regions exhibiting abnormal findings included the cingulate gyrus, an essential component of the pathophysiological basis for depression related to the makeup of the default mode network[56]. In clinical research, cingulate gyrus abnormalities have been reported in various psychiatric disorders[57]. Altered WM connectivity in adolescent depression patients has also been described[58], contributing to reduced default mode network connectivity closely related to depression incidence[59-61].

There are various drawbacks to this study. Firstly, the number of participants was relatively small, partly due to parental reservations about fMRI examinations. Secondly, the effects of resting state physiological noise derived from the heart and respiratory rhythms cannot be eliminated from these analyses. Lastly, this cross-sectional analysis could not detect disease progression-related changes in brain morphological characteristics, underscoring a need for future longitudinal research with multiple follow-up visits per patient to monitor better such changes and how they respond to treatment.

CONCLUSION

In summary, the present results demonstrate that adolescent depression patients exhibited various structural changes in the brain and altered CBF in the left pallidum and right PerCG. Considering the finding that the right PerCG demonstrated structural and CBF changes associated with depression in these adolescent subjects, research on the right PerCG may provide fresh perspectives on the pathophysiology of this devastating psychological disorder. This identification of novel evidence regarding changes in the cerebellum and other brain areas provides robust imaging evidence supporting the hypothesis that these regions are involved in cognition and disease-related pathogenesis. The future application of these findings has the potential to guide the better prevention and treatment of depression among adolescents.

ARTICLE HIGHLIGHTS

Research background

The prevalence of depression in adolescents is high and research is scarce. Therefore, it is urgent to investigate depressed adolescents.

Research motivation

In-depth neurobiological studies investigating the pathophysiology of depression are urgently needed to develop effective treatments to help adolescents escape the symptoms of this debilitating illness. Several studies have documented the role of the cerebellum in psychiatric disorders, which is rarely mentioned in the imaging of depression, emphasizing the need for further research on the depressed brain.

Research objectives

We aimed to detect structural and functional changes in depressed adolescents. These changes may be relevant to better prevention and treatment of adolescent depression. We found that adolescents with depression exhibit various structural changes in the brain and alter cerebral blood flow in the left syphilitic spiral and right percent gyrus.

Research methods

This study recruited 34 adolescents with depression and 34 matched healthy control (HC) individuals. Voxel-based morphometry (VBM) discovers structural changes in the brain; Cerebral blood flow (CBF)

explore functional changes in the brain; 17-item Hamilton Depression Rating Scale (HAMD-17) measures depression; *t*-test assess statistical differences.

Research results

We found that patients with adolescent depression exhibit various structural changes in the brain and altered CBF in the left pallidum and right percental gyrus. These findings may provide new insights into the pathophysiology of this disruptive psychological disorder and provide strong imaging evidence to support the hypothesis that these regions are involved in cognition and disease-related pathogenesis. Future applications of these findings have the potential to guide better prevention and treatment of depression in adolescents.

Research conclusions

New theory: Our study provides imaging evidence that supports the hypothesis that cerebellum is involved in cognition and disease-related pathogenesis. New method: We first combined VBM and CBF to examine the brains of depressed adolescents.

Research perspectives

Incorporating imaging data into the diagnosis of psychiatric disorders.

FOOTNOTES

Author contributions: Fu YJ and Liu X contributed to writing the original draft; Fu YJ and Liu X contributed to the work equally; Liu X, Wang XY, and Ren WY contributed to scanning magnetic resonance imaging data; Liu X analyzed the data; Li X and Dai LQ contributed to investigation; Zeng YM and Li ZL contributed to conceptualization and checking the data; Yu RQ contributed to methodology, and writing – review, and editing; All authors contributed to the article and approved the submitted version.

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Informed consent statement: The legal guardians of all participants provided written informed consent, and all participants were provided with a comprehensive overview of the details of the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at yurenqiang@hospital.cqmu.edu.cn. Participants gave informed consent for data sharing.

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LETTER TO THE EDITOR

Digital interventions empowering mental health reconstruction among students after the COVID-19 pandemic

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Abstract

With the gradual end of the coronavirus disease 2019 (COVID-19) pandemic, the reconstruction of students' mental health is urgently necessary. Digital interventions offer advantages such as high accessibility, anonymity, and accurate identification, which can promote the reconstruction of students' mental health through the provision of psychological support platforms, psychological assessment tools, and online mental health activities. However, we recognize that digital interventions must undergo many adjustments, and corresponding ethical norms require further clarification. It is crucial for different stakeholders to collaborate and work toward maximizing the effectiveness of digital interventions for the reconstruction of mental health after the COVID-19 pandemic.

Key Words: Digital interventions; Artificial intelligence; Big data; Students; Mental health

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Core Tip: As the coronavirus disease 2019 (COVID-19) pandemic has gradually come to an end, a challenge that has emerged is how to restore the mental health of students after the pandemic. This paper contends that digital interventions are cutting-edge and that effective approaches should be fully utilized to address the impact of the COVID-19 pandemic on the mental health of students.

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TO THE EDITOR

We have read the observational study titled "Investigating adolescent mental health of Chinese students during the coronavirus disease 2019 (COVID-19) pandemic: Multicenter cross-sectional comparative investigation" authored by Huang *et al*[1] and published in the 11th issue of the *World Journal of Psychiatry* in 2022. In this paper, the impact of the COVID-19 pandemic on the daily life and learning of adolescents was analyzed from four aspects: Time distribution, cohabitation groups, and positive and negative effects. The Patient Health Questionnaire-9 and the Generalized Anxiety Disorder Questionnaire- 7 were used to measure the impact of the COVID-19 pandemic on the mental health of adolescents. The results of the study indicated that there were significant differences in the time distribution of daily activities and cohabitation groups for adolescents before and after the COVID-19 pandemic. The academic performance of adolescents from different grades was negatively impacted by the pandemic, with distinct features observed for students at different grade levels; in particular, there was a significant increase in the rate of severe anxiety among junior high school students[1].

We believe that the conclusion of the article is highly valuable for discussion. The COVID-19 pandemic has greatly impacted the daily lives and learning of adolescents, and the mental health status of this population deserves more attention. Our previous research also showed that the prevalence rates of depression and anxiety among Asian university students range from approximately 20% to 40%[2,3], which are relatively high rates and have various negative effects on the daily lives of these students. Given the uniqueness of the COVID-19 pandemic, most studies suggest that the mental health of adolescents has shown a deteriorating trend during the pandemic[4,5]. Other studies have also reported results consistent with the findings of Huang *et al*[1], indicating that the incidence of mental disorders among adolescents, such as depression, anxiety, and stress, has decreased during the COVID-19 pandemic[6-8]. However, the mental health status of adolescents remains concerning. During the COVID-19 pandemic, the improvement of mental health among adolescents is often accompanied by an increase in attachment security and communication with parents, continuous optimization of organizational structures within schools, and gradual adaptation to daily life changes[7,9]. In our study, family, school, and individual factors were considered to be influencing factors of individual depression and anxiety levels, such as family relationships, parental education level, school environment, peer relationships, and lifestyle factors[2,3]. Therefore, general intervention measures should start from these three aspects, namely, enhancing family support for the mental state of adolescents, providing various forms of psychological counseling in schools, and adolescents themselves making efforts to maintain a positive attitude. These measures would improve the mental health status of adolescents during and after the COVID-19 pandemic.

Currently, there are abundant research findings on the impact of the COVID-19 pandemic on students' mental health. However, as the pandemic ends, it remains challenging to effectively address the mental health crisis caused by the pandemic and reshape positive mindsets in individuals. Digital therapy is emerging rapidly and gradually becoming a hot topic in the research and practice of mental health interventions. Digital interventions, carried out *via* the internet, big data, and artificial intelligence, provide a new form for screening, assessing, intervening and treating mental health problems[10,11]. Several studies have confirmed the effectiveness of digital interventions in the treatment of mental health[12-15]. Their advantages are mainly reflected in the following three aspects. First, digital interventions are highly accessible, which can alleviate the imbalance between the supply and demand of mental health services[16,17]. The COVID-19 pandemic was characterized by a sudden onset, long duration, and broad impact. The resulting mental health problems have become increasingly prominent, and many professional psychologists are needed to provide targeted mental health services. In fact, the public health system has a limited capacity to respond to emergencies, and mental health resources are limited[18]. In the context of the intelligence era, students can access various forms of digital intervention services through the internet and mobile platforms to address potential mental health problems in a timely manner[19]. Second, digital interventions are anonymous, which can reduce the risk of stigmatization. Due to concerns about stigmatization, many students have low willingness to seek psychological help, and their anxiety and depression may not be relieved in a timely manner[20]. With the use of digital interventions, students can access services anonymously at any time[21]. Third, digital interventions can accurately identify psychological health problems and provide effective solutions. Through health data tracking and intelligent analysis systems, digital interventions can accurately screen students with potential psychological health problems, making it easier to provide psychological counseling in a timely manner. In addition, based on the different needs of students, digital interventions can also provide personalized psychological support, making them more flexible and convenient to use[16,22].

It is worth noting that there are still some challenges in more extensive and efficient mining and application of digital psychological health interventions. First, students inevitably face the risk of information leakage when using applications and other mobile platforms. Various countries have not established an effective supervision and management system, and the corresponding ethical norms need to be further clarified[23,24]. Second, digital interventions are essential tools. Psychological health practitioners should combine their professional literacy and fully utilize the characteristics of digital technology to maximize the potential of digital interventions[25]. Finally, technology changes rapidly,

and digital psychological health interventions have not kept up with the pace[18]. Different stakeholders need to work together to inject new vitality into digital psychological health interventions using the latest artificial intelligence and virtual reality technologies.

The rapid development of artificial intelligence provides powerful support for the improvement and popularization of mental health services. In response to the challenges encountered in the application of digital psychological interventions, the latest research proposes suggestions from three aspects: Theory, practice, and future development trends. First, the theoretical foundation for the development of digital intervention needs to transform good clinical practice standards (such as CBT) into key components of mental health services[26]. Second, to improve the effectiveness of digital psychological interventions, a participatory design approach should be widely adopted[27], and cultural relevance should be integrated into mobile applications or online platforms[28,29]. Finally, future digital psychological interventions should fully utilize the latest developments in artificial intelligence, applying algorithms such as machine learning and deep learning to automatically identify and analyze emotional states and establish a mental health database. In addition, protecting user data privacy, reducing costs, and improving usability are also key issues that need to be addressed in the future[30,31]. Regarding the protection of user privacy, we believe that students' information literacy should be given attention. In the digital environment, students are vulnerable to data malfunctions and the unethical use of their data. To prevent this situation, students should be aware of the risks they may face in digital media, improve their digital literacy and safety awareness, effectively use and manage their digital archives, and have a healthy online/offline social life.

In conclusion, after the outbreak of the COVID-19 pandemic, restoring the mental health of students is urgently necessary. Digital interventions can promote the reconstruction of students' mental health by providing a platform for psychological support, offering psychological assessment tools, and facilitating online mental health activities. We believe that digital interventions should be actively adopted to support students' mental health and enhance social welfare.

FOOTNOTES

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OPINION REVIEW

Not one thing at a time: When concomitant multiple stressors produce a transdiagnostic clinical picture

Sari Goldstein Ferber, Gal Shoval, Aron Weller, Gil Zalsman

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Abstract

A condition of exposure to multiple stressors resulting in a mixed clinical picture spanning conventional categories without meeting any of them in full, encompasses a risk for a list of comorbidities preventing appropriate prevention and treatment. New transformative transdiagnostic approaches suggest changes spanning conventional categories. They base their systems of classification on biomarkers as well as on brain structural and functional dysregulation as associated with behavioral and emotional symptoms. These new approaches received critiques for not being specific enough and for suggesting a few biomarkers for psychopathology as a whole. Therefore, they put the value of differential diagnosis at risk of avoiding appropriate derived prevention and treatment. Multiplicity of stressors has been considered mostly during and following catastrophes, without considering the resulting mixed clinical picture and life event concomitant stressors. We herewith suggest a new category within the conventional classification systems: The Complex Stress Reaction Syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post coronavirus disease 2019 era, in the general population. We argue that this condition may be relevant to daily, regular life, across the lifespan, and beyond conditions of catastrophes. We further argue that this condition may worsen without professional care and it may develop into a severe

mental health disorder, more costly to health systems and the suffering individuals. Means for derived prevention and treatment are discussed.

Key Words: Transdiagnostic; Multiple stressors; Clinical picture; Prevention; Treatment; Interpersonal psychotherapy; Cognitive behavioral therapy

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Core Tip: Multiplicity of stressors has been considered mostly during and following catastrophes, without considering the resulting mixed clinical picture and life event concomitant stressors. We herewith suggest a new category within the conventional classification systems: The Complex Stress Reaction Syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post coronavirus disease 2019 era, in the general population. We argue that this condition may be relevant to daily, regular life, across the lifespan, and beyond conditions of catastrophes.

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INTRODUCTION

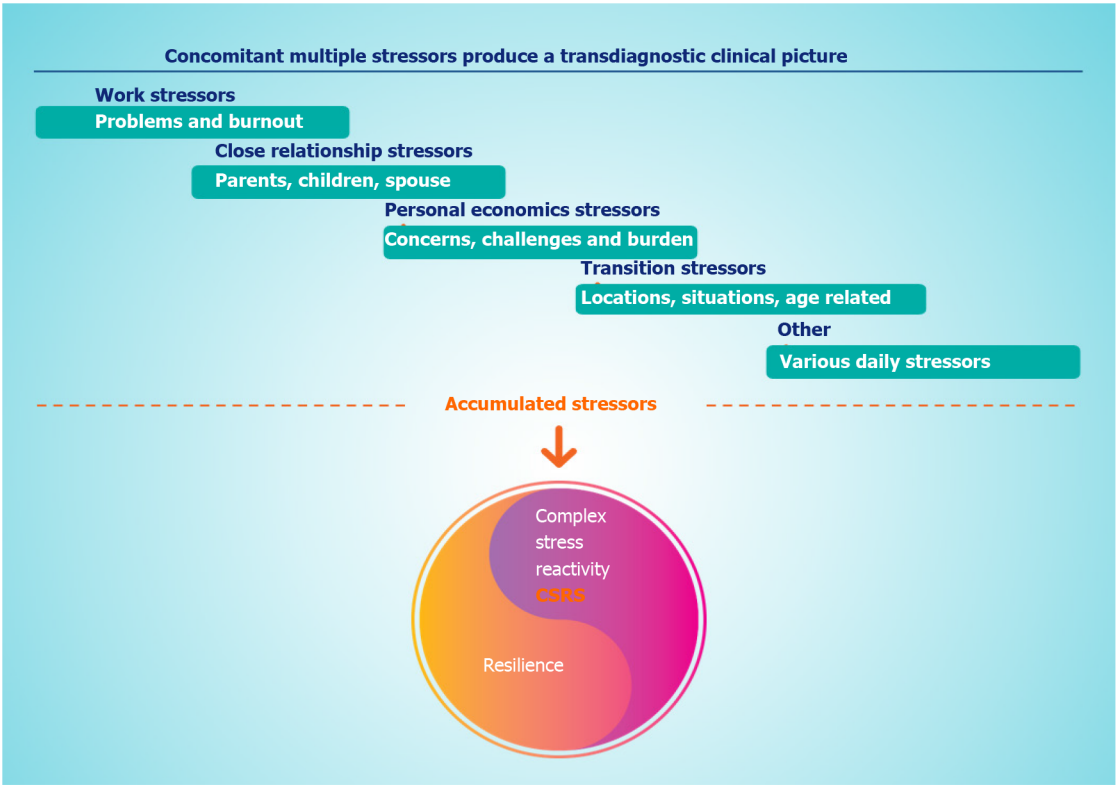
Many people with mental health complaints present a mixed clinical picture. Often none of the com-plaints meet the full criteria of any of the conventional classifications. Possibly, several categories are met (though not completely), leading to a list of comorbidities. This precludes clear diagnosis, preven-tion and treatment.

There are at least 4 different suggestions to revise classical classifications into transdiagnostic appro-aches: Hierarchical Taxonomy to Psychopathology[1], Research Domain Criteria[2], Bipolar-Schizophrenia Network on intermediate phenotypes[3,4], and Neuroscience-Based Nomenclature[5]. These suggested new classification systems are based on neuroanatomic findings showing that several brain areas demonstrate similar functionality and structure in various conventional categories[6-9]. However, others have commented on these data that they lack specificity, as the biomarkers show relevance over too many mental disorders[10]. Thus, many current conventional classification categories are gathered in the transformative systems into one pool of psychopathology, preventing consequent application of accurate prevention and treatment per each disorder including the missing clinical attention to indivi-dual differences.

Part of the mixed clinical pictures involves the concomitant experience of multiple stressors. As it arises from our literature search using PubMed, Google Scholar and *Reference Citation Analysis* (RCA), the impact of multiple stressors has been discussed by cutting edge papers mostly in the context of disasters such as hurricanes, floods, wars and in drastic conditions experienced by refugees and immi-grants including the coronavirus disease 2019 (COVID-19) era, with similarities between the impacts in these types of conditions across the lifespan, *e.g.*[11-14]. The most common psychiatric outcomes reported are post-traumatic stress disorder (PTSD) and depression[15-20]. There are scarce reports on multiple stressors in daily life as related to the development of psychiatric disorders. Some of these reports relate to stressors in the workplace, economic hardships and the impact of urbanization[21-23]. Surprisingly, here also PTSD and depression are the common outcomes. The diagnosis of these two disorders in such different types of multiple stressors calls for attention and re-evaluation. Thus, the aim of the current paper is to suggest a new potential category for the conventional diagnostic system, which will include conditions of mixed clinical pictures with more than one stressor identified.

As clinicians, we encountered a condition in which many patients showed mixed symptomatology, spanning conventional categories, without fully meeting all the conventional criteria of any of these categories during the multi-stressor COVID-19 outbreak. Our literature review supported our observa-tions[24]. In a following empirical bi-national study, using representative, large samples[25], we further found that combinations of several mental health symptoms studied, PTSD, phobia, depression, anxiety and posttraumatic stress symptoms, were more prevalent than combinations of fewer symptoms, with no majorities-minorities differences in both Italy and Israel[25]. We termed this mixed clinical picture the Complex Stress Reaction Syndrome (CSRS). CSRS includes type A (a psychiatric part) and type B (a neuropsychiatric part for the long-COVID component, excluding systemic symptoms)[24,25]. As more cross-cultural studies of the CSRS are warranted, we are currently conducting such an international study with participants from 8 diverse countries located in the Middle East, Europe, Australia and North America.

In this paper we suggest that the CSRS type A (the psychiatric part, not including type B) may explain mixed clinical pictures in conditions of multiplicity of significant stressful life events in the post-COVID era. Thus, we argue that in the general population, experiencing concomitant multiplicity of life events-related stressors may account for the development of a mixed type of mental health disorder, not only in conditions of catastrophes (see Figure 1).



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Figure 1 Accumulated stressors in daily life are associated with a mixed clinical picture in the general population. CSRS: Complex Stress Reaction Syndrome.

Differential diagnosis

For differential diagnosis, the CSRS (type A) may be compared to: (1) Diagnosis of adjustment disorder rules out PTSD and bereavement, and it displays a short stressor onset-symptoms occurrence latency; (2) PTSD diagnosis includes exposure to one frightening stressor; (3) Obsessional thoughts are ego-syntonic by definition. The behaviors related to extrinsic stressors are clearly not included in the obsessive-compulsive disorder (OCD) conventional category; (4) Diagnosis of acute stress disorder implies a simpler stressor and a specific symptom response; (5) The criteria for defining generalized anxiety disorder list excessive worrying (on diverse issues) and shifting back and forth among them, thus not implying the multiplicity of stressors and a mixed clinical picture; (6) The diagnosis of major depression disorder includes anhedonia, low affect, psychomotor agitation, unfitting guilt feelings, diminished drive and energy, trouble concentrating, and indecisiveness with no other types of symptomatology which are included in a mixed clinical picture; and (7) C-PTSD is described as the result of a series of traumatic events, which is repetitive and hard to escape but does not include a mixed clinical picture beyond the PTSD conventional criteria. It also describes a series of events and not the simul-taneous occurrence of multiple stressors as the possible etiological source for psychopathology.

Prevention

The impact of multiple concomitant stressors depends on individual subjective perception and stress reaction tendencies [26]. The immediate question is what can prevent the emergence of pathological stress reactions, spanning several conventional categories. In a previous study we found that close relationships may protect the individual across the types of psychopathology investigated, spanning anxiety, depression, PTSD and OCD criteria, in conditions of multiple stressors[27]. The means for illness prevention and enhanced coping are therefore suggested as keeping close relationships active. Public and media educational programs for conditions of multiplicity of life stressful events with transdiagnostic potential consequences, aimed at enhancing individual resilience by utilization of social networks, are herewith suggested, evidence-based[27,28].

Treatment

We suggest a combined treatment approach of interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CBT), two evidence-based and cost-effective methods, designed as short-term thera-pies and found to be equally effective to medications[29] in comparative studies[30,31]. Enhanced close relationships by techniques of problematic interpersonal relations analysis, resolution and role playing adapted from IPT[32], may increase emotional tolerance to accumulating stress emerging from conco-mitant origins. Our suggested combined psychotherapeutic approach also requires the blending of CBT separate protocols, including techniques for stress reduction and correction of cognitive distortions, rather than following one protocol separately or as recently suggested, one mandatory unified protocol for all

types of symptomology[33-36].

We suggested previously that when exposed to multiplicity of stressors, the lack of clear goals implies the diffusion of actions[37]. This could be a risk factor for effective treatment of patients confronted with this type of condensed stressful experience. To overcome this risk and also to respect individual differen-ces, a patient-specific and session-specific therapeutic strategy of assigning clear goals for adaptive coping is warranted, rather than working through a reparation condition or just attempting to eliminate the identified external stressors.

DISCUSSION

The origins of CSRS

The CSRS emerged from the robust transdiagnostic clinical pictures during and following the pandemic[38]. The World Health Organization indicates a prevalence of 22% of a mixed picture including depre-ssion, anxiety, PTSD, and general distress, fatigue, irritability and anger in the general population fol-lowing the experience of war or natural disaster[39]. Transdiagnostic approaches to classifications were proposed even prior to the COVID-19 pandemic[1-4]. Here we argue that the impact of multiple stre-ssors in daily life is a neglected issue in traditional classifications.

What was probably different about the COVID-19 pandemic compared to previous catastrophes was its global scale and the fact that it was covered extensively by the social, electronic, and print media. This factor may be regarded as an additional stressor in daily life beyond disasters. Whether media use is a source of social support, especially for young people[27,40,41] or a daily life stressor in the form of bom-bardment of information[42], is still a topic under scientific debate and probably age-related with large inter-individual variance.

Although there is enough evidence to suggest that the mental health of the population deteriorated following the pandemic[43], there are suggestions that the extent of deterioration was less than anticipated[44,45]. In any case, epidemiological studies have shown that anxiety, depression, functional somatic, and even obsessional symptoms can coexist at the population or the community level[38,46,47], supporting our transdiagnostic views and the CSRS.

Inclusion of long COVID symptoms in the CSRS may create the same psychological *vs* physical dispute that we have witnessed with chronic fatigue syndrome or myalgic encephalomyelitis, but we include in the CSRS just neuropsychiatric symptoms, while systemic components of long COVID are excluded. In support of our view, studies that have already started appearing suggest that the long COVID syndrome is more likely to be associated with psychosocial factors rather than the COVID infection itself[48].

Thus, the origins of CSRS are rooted in the multi-faceted stress of the pandemic and its impact on mental health including its residuals in the post COVID era. The relevance of concomitant stressors included in daily life, under regular, non-catastrophic conditions, and their association with a mixed clinical picture, is gradually becoming apparent.

The CSRS within the debate on psychiatric nosology

Our opinion goes beyond conventional approaches for construction of psychiatric taxonomy. Alter-native concepts of psychiatric validity include controversies between validation of nosological struc-tures (typical for medicine) as compared to prototype, cluster and dimensional diagnosis of mental disorders[49]. While the field of psychiatry moved towards more medically oriented nomothetic knowledge, alternative groups which we follow in our empirical and review papers, suggest that the field has to move away from this type of knowledge towards a more ideographic and subjective appro-ach to psychopathology[49].

The main differences between the validity of dimensional diagnostics and that of traditional nosology are apparent in several aspects: (1) In traditional approaches, mental pathology is regarded as a strict drift from acceptable norms while the transdiagnostic views, similar to ours, suggest an axis between normal and psychopathological conditions; (2) In dimensional approaches co-existing psychopathological states appear in parallel along with personal strengths and capacities for resilience, unlike traditional nomenclature; (3) Dimensional approaches to the convergent and divergent validity of a cluster or co-existence of different pathologies without meeting a full criteria of any category in the conventional systems, such as the CSRS, do justice to the patient and the entire individual clinical picture he or she describes to the clinician, while traditional approaches prefer multiple comorbidities; and (4) The dimensional approaches such as the CSRS, unlike conventional systems, emphasize subjec-tive complaints of the patient (symptoms) rather than signs judged by the clinician. By that, these dimensional approaches are shifting the focus from the powerful societies of professionals towards the patient's subjectivity, and they recognize that professionals too, have their own subjective perspectives to consider before endorsing a diagnosis based only on signs.

Specifically, the CSRS has shown high reliability, as in two different countries and with two different methodologies similar results were found[25]. Additionally, the CSRS has shown high convergent and divergent validity as a combination of several identified stress symptoms, without meeting any full conventional category. These findings suggest a complex and unique type of reactivity to multiplicity of stressors. Other combinations suggested earlier, as complex anxiety and depression[50] or complex post traumatic stress disorder, showed validity for inclusion of just two conventional categories[51] while others showed a too wide range of inclusion, ruling out the potential judgement of divergent validly[10].

We acknowledge the importance of biological validation of psychiatric illness, but this still cannot be utilized for a treatment per any specified condition until the field of neuropsychiatric science advances considerably. The CSRS implies symptoms more than signs and subjectivity more than objectivity. The treatment derived from the CSRS would be patient-specific and session-specific, as human experience may go back and forth on the axis of elevated symptomology *vs* resilience and adaptive coping. There-fore, the notion of session-specific treatment requires the clinician's diagnostic

effort at every given session to reevaluate the patient's symptomology for progression *vs* regression and to offer treatment accordingly. We propose that the human experience transits along time that elapses and a condition may be judged for a given patient, in a given environment at a given moment, considering how the observed syndrome has been individually experience-shaped[52-55].

It was noted earlier that the empirical validation used as the basis of conventional categories has been mostly regression statistical analyses with a weak basis for causality[49]. Contrary to any etiological arguments, we argue that the CSRS represents an association between multiplicity of stressors and a mixed clinical picture, which is worth treating to avoid further increase in the patient's stress reactivity and future limitations of his or her resilience capacities.

We locate CSRS within the blend of the biopsychosocial model (BPS)[56] and the person-centered medicine (PCM) approach[57], as the novel CSRS is related to exogenic stressors (BPS) and occurs as a subjective complex stress reaction of the patient (PCM). Thus, as outlined here and according to our bi-national research design and findings[25], the CSRS falls within the post-modern dimensional appro-aches more than within any strict nosology, for better prevention and treatment. CSRS was designed and investigated from a humanistic perspective, arguing that mental health is not represented by the lack of psychopathology, while psychopathology, in turn, is a condition with an indication to treat and may be reversible.

CONCLUSION

Transdiagnostic considerations towards a change in the classification of mental disorders can be accom-plished within the existing systems without ruling out the importance of differential diagnosis if these conventional systems will start to include transdiagnostic phenomena as legitimate conditions for treatment and care. This reduces the risk of diagnosing too many comorbidities and by that precluding appropriate prevention and treatment. We argue that the syndrome termed as CSRS better identifies those patients reacting in a manner that spans several conventional diagnostic categories following exposure to concomitant multiple stressors. Unlike approaches that argue for complete transformation of conventional classifications[1-5], we claim that that a specific diagnosis concerning multiplicity of stressors that result in a mixed clinical picture, is a potential contribution to the revised Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases for more accurate derived prevention and treatment. The future will tell if the openness to include post-modern transdiagnostic approaches to accurately serve more patients in need and to facilitate clinical practice of each individual psychiatrist, will be part of the discussions on the next revisions of the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases or whether the debate and crisis in psychiatry[58] will continue.

FOOTNOTES

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MINIREVIEWS

Delivering substance use prevention interventions for adolescents in educational settings: A scoping review

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Abstract

Currently, a proportion of adolescents use alcohol, tobacco, and illicit drugs, which inevitably harms their health and academic progress. Adolescence is a peak period for substance use initiation and a critical time for preventing substance use problems. Various entities, such as families, schools, and communities, have implemented a variety of interventions to alleviate adolescent substance use problems, and schools play a unique role. To explore the types, characteristics, and effectiveness of substance use interventions in educational settings for adolescents, we conducted a scoping review and identified 32 studies after screening. We divided the 32 studies according to intervention type, including curriculum interventions focusing on cognitive-behavioral skill enhancement, exercise interventions, peer interventions and family-school cooperation, and electronic interventions. Except for the mixed results on electronic interventions, the results showed that the other interventions were beneficial to different extents in alleviating adolescent substance use problems. In addition, we analyzed and summarized the advantages and challenges of intervening in adolescent substance use in educational settings. Schools can use equipment and human resources to provide adolescents with various types of intervention measures, but they also face challenges such as stigmatization, ineffective coordination among multiple resources, and poor implementation effects. In the future, school-based intervention measures can fully utilize big data and artificial intelligence technology and collaborate with families and communities to intervene appropriately while paying attention to the comorbidity risks of substance use disorders and psychological health issues.

Key Words: Substance use; Prevention; Adolescents; Educational settings; Artificial intelligence; Digital interventions

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Core Tip: Interventions in educational settings include curriculum interventions, physical activity interventions, peer interventions and family-school cooperation, and electronic interventions. Except for the mixed effectiveness of electronic interventions, all other intervention measures are beneficial in alleviating substance use problems among adolescents. Schools can utilize equipment and human resources to provide various types of interventions but also face challenges such as stigmatization and ineffective coordination between multiple resources. In the future, schools can fully utilize big data and artificial intelligence technologies, jointly intervene with families and communities, and appropriately address the comorbidity risks of substance use disorders and mental health issues.

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INTRODUCTION

Currently, substance use and abuse among adolescents have become important global public health issues. Adolescence is a critical period for physical and psychological development, as well as for experiencing life, pursuing independence, and establishing intimate relationships[1]. Individuals are more susceptible to substance use risks in the adolescent stage than in other stages of life. Research has shown that adolescence is the peak time for the initiation of drug use[2]. The level and frequency of drug use among adolescents begin to increase in mid-adolescence and peak in early adulthood. The median age of onset of alcohol use in most countries is 16-19 years[3]. The global burden of disease study showed that drug use is a significant factor in the health burden in the adolescent and young adult population[4]. Early exposure to alcohol, tobacco, and other drugs may lead to violent or aggressive behavior in adolescents, making it difficult for them to adapt to school, family, and social environments[5]. Such exposure not only causes various negative health outcomes [1], but may also result in psychological health issues such as anxiety and depression in adolescents[6-9]. Therefore, it is essential to identify substance use problems in the adolescent population as early as possible and to take timely intervention measures.

Multiple research results indicate that adolescent substance use problems are the result of the combined action of various risk factors, such as personal, family, school, community, and societal factors. Substance use by parents or relatives in the family environment has an insidious influence on adolescents while also providing a channel for their substance exposure[10]. Adolescents who are in disadvantageous positions in life are more likely to use drugs to escape the pressure of reality[11]. Peer substance use in the school environment may stimulate the curiosity of adolescents or cause them to use drugs to fit in due to "peer pressure"[12]. Implementing intervention plans based on different subjects is an effective strategy to address adolescent substance use problems[13-16]. First, at the social level, clearly defining the scope of legal substance use and adopting strict regulatory measures can effectively reduce adolescents' negative substance use behavior[17]. For example, alcohol or tobacco price controls can be implemented through taxes[18-22], minimum age laws can be enforced[23], and the availability of inhalants can be minimized[24]. Second, at the family level, factors such as parenting style, family relationships, and family function can significantly predict adolescent drug abuse and related behaviors[25]. Family involvement has been found to be effective in treating adolescent substance use disorders. The basic principle of family-based intervention measures is to directly or indirectly establish more stable family relationships by providing training courses or developing intervention plans for parents and adolescents, thereby reducing the risk of adolescent substance use disorders[26-28]. For example, the Strong African American Families-Teen program effectively prevents drug use and emotional problems in black adolescents by offering 10 h of adolescent skills training courses and family courses[29]. Family matters (FM) helps parents identify family characteristics, behaviors, and attitudes that may affect adolescent drug use by regularly mailing families guidance manuals. Professional health education workers follow up on the use of the manuals by contacting parents after each mailing. The results of a study on FM showed that the complete intervention plans effectively reduced the rates of tobacco and alcohol use in adolescents [13]. Third, at the community level, some studies suggest that the community and its surrounding environment can play a positive role in adolescent substance use problems[16,30]. Community-based intervention plans usually require community leaders, community workers, and other stakeholders and professionals to work together. For example, in the Community Trials Intervention to Reduce High-Risk Drinking, community leaders use local policies and regulations to control the number of bars, retailers avoid selling alcohol to minors, and so on[13]. Clearly, intervention measures based on multiple stakeholders, such as those at the social, family, community, and school levels, can play an essential role in resolving adolescent substance use problems[16]. Multidimensional family therapy (MDFT) integrates family therapy, individual therapy, and drug counseling with multisystem intervention methods[31]. Multiple experiments have shown that MDFT is a more effective treatment method than other methods for adolescent drug abuse and comorbid mental symptoms[32].

In addition, as current adolescents are "digital natives", they have a "natural" attraction to digital interventions[33-35]. Technology-based intervention measures are mainly interactive digital activities aimed at preventing or delaying adolescent drug use from the aspects of knowledge, attitude, and behavior[36-38]. RealTeen is a web-based intervention measure that places youth in realistic drug use scenarios by using interactive skills-building sessions. Adolescents can

improve their self-awareness and social skills, thereby avoiding drug use[39,40]. Studies have shown that after intervention, participants have lower rates of use of alcohol, marijuana, and multiple drugs[39]. Specific intervention measures based on multiple subjects are shown in Table 1.

Compared with other context, such as families and communities, the educational environment in schools offers unique advantages for intervening in adolescent substance use. Considering the characteristics of adolescence, such as a long duration of schooling, close peer interaction, and intensive education, schools are an excellent place to intervene in adolescent substance use[1]. On the one hand, school can educate adolescents on the characteristics and harms of the use of substances, such as alcohol, tobacco, and illegal drugs, by offering relevant courses. On the other hand, peer interaction and practical activities in the school environment can make adolescents value education, help them form a correct attitude toward life, and prevent substance use problems before they happen[41,42].

Recent research has focused on the importance of schools in addressing adolescent substance use problems and exploring effective intervention measures from different perspectives. For example, intervention models have been constructed based on cultural backgrounds and family relationships, Botvin Life Skills Training has been used to train students in the school environment, and psychological training has been implemented to prevent substance use problems among adolescents. These measures aim to improve adolescent tobacco use problems[43-45].

The existing literature has proposed various intervention measures based on the seriousness of adolescent substance use problems. However, the vast majority of research only discusses school-based intervention as one of many intervention measures[46], and few studies have directly investigated preventive intervention measures for adolescent substance use from the perspective of the educational environment. Considering the changes in adolescent substance use problems before and after the pandemic, this paper, based on a comprehensive review of existing literature in this field, focuses on research results from the past seven years and further explores preventive intervention measures for adolescent substance use in the educational environment.

Objectives

Based on the unique advantages of schools in intervening with adolescent substance use and the richness of research in this field, we conducted a scoping review to understand specific intervention measures and their effectiveness in the current educational environment. Our research questions were as follows: (1) What are the intervention measures currently used in the educational environment to intervene with adolescent substance use? and (2) what are the characteristics and effects of these intervention measures?

LITERATURE REVIEW

Search strategy

To explore the types, characteristics, and effectiveness of intervention measures for adolescent substance use in the educational environment, we conducted a preliminary evaluation of relevant literature in this field. Literature searches were conducted in May 2023 in five databases: Web of Science Core Collection, PubMed, EBSCO, Scopus, and Google Scholar (selecting the top 200 most relevant articles). The following keywords and terms were used: (1) Substance use; (2) adolescent; (3) educational setting; and (4) prevention. The following string was used: ("substance use" [All Fields] OR "alcohol" [All Fields] OR "tobacco" [All Fields] OR "marijuana" [All Fields] OR ("illicit drug" [All Fields]) AND ("youth" [All Fields] OR "teenager" [All Fields] OR "adolescence" [All Fields]) AND ("school" [All Fields] OR "educational setting" [All Fields]) AND ("intervention" [All Fields]) OR "prevention" [All Fields]).

Study selection

The full screening process included three stages: (1) EndNote software was used to identify duplicate articles and retain those with more comprehensive information; (2) the first round of screening was conducted based on the inclusion and exclusion criteria, along with titles, abstracts, and keywords in EndNote; and (3) manual screening was performed based on the full text using Rayyan.

The inclusion criteria were as follows: (1) The age of the study subjects was 10-19 years (according to UNICEF, WHO, and UN Population Fund); (2) intervention measures were based in educational settings; (3) there was a specific, clear, and operational intervention plan for substance use problems; (4) the article was easily accessible; and (5) the article was published in English.

The exclusion criteria were as follows: (1) The age of the study subjects was outside the defined range; (2) intervention measures were based on other environments, such as family and community; (3) the article did not belong to the substance use problem category or only mentioned the topic briefly; (4) the article was a literature review, letter to the editor, or opinion piece; (5) the article was from the gray literature; and (6) the article was published in a language other than English. Please see Figure 1 for the specific screening process.

Data analysis

After screening, a total of 32 articles were obtained. Analyses and table summaries of the literature revealed that these articles could be grouped based on the type of intervention strategies used. The two primary themes and their associated subthemes are as follows: (1) Various types of intervention strategies and their effects include interventions that focus on cognitive-behavioral skill building, exercise, peer and family involvement, and electronic interventions; and (2) differences in substance use intervention strategies among adolescents in different educational stages.

Table 1 Multiagent-based adolescent substance use interventions

Implementation subject	Intervention method	Specific measures
Based on social intervention measures	Clarifying the scope of legal substance use and adopting strict regulatory measures	Manage the age, sales timeframe, permissible quantities, and pricing of substances and regulate users[18]
		Levy taxes on the alcohol or tobacco content of goods and tie them to fluctuations in consumer pricing[19]
		Implement and enforce laws mandating a minimum age limit and raise the age threshold for young people to purchase alcoholic beverages[18,23]
		Create community-specific regulations concerning the issuance of tobacco and alcohol licenses to minors and promote their enforcement within localities[24]
Based on family intervention measures	Providing training courses for parents and teenagers	Strong African American Families-Teen program: Deliver skill-building courses and family training sessions spanning 10 h and comprising 5 sessions to both parents and teenagers[29]
		Creating lasting family connections: Offer a 20-wk facilitator training program for parents and teenagers[13]
	Developing intervention plans	Families preparing the new generation plus: Execute a 10-wk prevention plan for nutrition and material use while emphasizing healthy eating and parenting strategies[26]
		Familias Unidas: Enforce a set of intervention measures aimed at enhancing parents' sense of efficacy and parenting skills (parent support networks), family meetings/home visits, parent-adolescent discussion circles, adolescent activity groups, supervised peer activities, and school counselor meetings)[27]
		Risk reduction therapy for adolescents: Intervention measures conducted by a professional therapist with a relevant master's degree at an outpatient clinic. Caregivers are obligated to attend a weekly session lasting between 60 min and 90 min[28]
Based on community intervention measures	Providing community intervention programs	Community trials intervention to reduce high-risk drinking: To modify the community's drinking behavior, offer responsible beverage service, reinforce law enforcement, and set up alcohol checkpoints[13]
		Deliver a 10-wk intervention plan for adolescents using the Health Rocks program and multiple disciplinary literacy strategies. Emphasize the effects of substance abuse on health and require adolescents to attend a one-hour theme-based instruction per week[30]
Based on technology intervention measures	Utilizing innovative intervention methods, such as the internet and big data	CLIMATE: Provide 6 lessons based primarily on social influence theories *via* CD-ROM and the Web. The lessons provide knowledge about how common substance use is as well as the negative outcomes it can lead to and teach methods to avoid substance use and the subsequent hazards[37]
		HeadOn: Require the involvement of students in decision-making related to substance use through interactive simulation scenarios[38]

LITERATURE RESULTS

Each section summarizes the mechanism and effects of various intervention measures (Tables 2-5).

Various types of intervention measures and their effects

Curriculum interventions focused on cognitive-behavioral skill enhancement[47,48]: The mechanism of these interventions involved two parts (Table 2): (1) Using traditional ethnic values and methods to prevent smoking, drug use, *etc.*[49] and connecting the psychological and social concepts of substance use with multicultural values[50] to regulate adolescent substance use behavior; and (2) implementing a series of courses to improve students' cognitive and behavioral skills[51], including knowledge about the characteristics and harms of alcohol, tobacco, and illicit drugs[52], communication[53], decision-making and other life skills[54,55], and methods to resist drug use pressure[56,57]. These interventions had positive effects on adolescent alcohol, cigarette, and marijuana use to varying degrees. A study conducted a randomized field trial with seventh- and ninth-grade students to implement a school-based intervention program, Take Charge of Your Life (TCYL), to prevent adolescent alcohol, tobacco, and drug use. The TCYL program follows the principles of substance abuse prevention programs, using counseling classes to help students understand the negative effects of alcohol, tobacco, and illicit drugs on individuals and society, and it requires students to learn communication, decision-making, assertiveness, and refusal skills. The results of the study showed that TCYL helped reduce the potential motivation for drug use and was beneficial for students who smoked marijuana[58] (Table 2).

Exercise interventions: Exercise is one of many health behaviors associated with good lifestyle habits[59]. Exercise programs to intervene in adolescent substance use problems help adolescents develop good lifestyle habits to reduce the willingness to engage in substance use and the frequency of substance use[60,61]. Werch *et al*[62] and Goldberg *et al*[63] primarily used exercise screening, counseling, and exercise training courses to reduce adolescent drinking behavior and improve health habits. More recently, new forms of exercise intervention have emerged in schools. Some examples

Table 2 Curriculum interventions focusing on cognitive-behavioral skill enhancement

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Diaz Gomez *et al*[47], 2021	10-12 yr, all genders	Yes	Yes	-	Randomized controlled cluster study	Primavera is a prevention program that focuses on experiences and involves multiple modes of delivery. It spans several years and has a generic approach	Primavera is effective in decreasing alcohol consumption among school students	France
Kimber *et al*[48], 2009	Grades 7 to 9 (13-16 yrs), all genders	Yes	Yes	Yes	Nonrandomized five-year longit-udinal design	Teachers offer weekly lessons on social and emotional training to students	A particular group of people derived benefits from the program	Sweden
Hecht *et al* [49], 2003	Grade 7, all genders	Yes	Yes	Yes	Randomized controlled trial	Interventions based on culture are conducted through 10 specific lessons and a media campaign utilizing a model of cultural resilience	The intervention had a considerable and noteworthy effect on individual consumption of alcohol, cigarettes, and cannabis	United States
Unger *et al* [50], 2004	Grade 6, all genders	-	Yes	-	Participatory research	The Project Fun Learning About Vitality, Origins, and Respect is a curriculum that promotes multicultural education	The project successfully stopped hispanic boys from starting smoking but had no impact on other groups	United States
Walker *et al*[51], 2011	14-19 yr (Grade 9-12), all genders	-	-	Yes	Randomized controlled trial	Motivational enhancement therapy, educational feedback control, and delayed feedback control	Participants stated that they used cannabis less frequently and experienced fewer negative outcomes	United States
Faggiano *et al*[52], 2010	12-14 yr, all genders	Yes	Yes	Yes	Cluster randomized controlled trial	The program involved a 12-h curriculum that was developed using a thorough social influence approach	Alcohol abuse and marijuana use showed a consistent improvement, whereas smoking displayed no change	Spain, Belgium, Germany, Sweden, Greece, Italy, and Austria
Dent *et al* [53], 2001	14-17 yr, all genders	Yes	Yes	Yes	Randomized controlled trial	Project Toward No Drug Abuse: Standard care and classroom education program	Over a period of one year after the program, this population saw statistically significant changes in alcohol and illicit drug use	United States
Hanewink *et al*[54], 2004	Grades 5 and 6 (mean age 11.4 yr), all genders	-	Yes	-	Randomized controlled trial	The smoking prevention program utilized a life-skills approach and included 21 sessions	The program did not have a distinct impact on the current smoking rate (percentage of people who smoked in the past 4 wk)	Austria, Denmark, Luxemboug, and Germany
Botvin *et al* [55], 2001	Grades 7 to 9, all genders	Yes	-	-	Randomized controlled trial	A proactive approach that educates individuals on resisting alcohol and drug consumption, promoting healthy social norms, and providing material to encourage personal and social skill-building	The prevention program was effective in protecting against episodes of excessive drinking	United States
Botvin *et al* [56], 1999	Grade 7 (mean age 12.9 yr), girls	-	Yes	-	Randomized controlled trial	This program consists of 15 sessions aimed at teaching social resistance skills within a broader initiative that aims to promote general personal and social competence skills	The number of urban minority girls who started smoking or increased their smoking habits was significantly reduced	United States
Shope *et al* [57], 1998	Grade 6 (mean age 12 yr), all genders	Yes	Yes	Yes	Participatory research	The students in the curriculum group were taught about alcohol, tobacco (including cigarettes and smokeless	The curriculum achieved short-term effectiveness by considerably decreasing the rising rates of alcohol	United States

						tobacco), marijuana, and cocaine	consumption and addiction, tobacco use, cocaine intake, and other types of substance abuse	
Sloboda *et al*[58], 2009	Between seventh and ninth grade, all genders	Yes	Yes	Yes	Randomized field trial	TCYL offers students essential life skills, which include communication, decision-making, assertiveness, and refusal skills	TCYL had a negative impact on students' use of alcohol and tobacco as a result of medical treatment	United States

TCYL: Take charge of your life.

Table 3 Exercise interventions

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Werch *et al* [59], 2005	Ninth and eleventh grade, all genders	Yes	Yes	Yes	Randomized controlled trial	Project SPORT is a short intervention that promotes healthy habits by integrating physical activity and preventing alcohol use	After the treatment and after one year, it was anticipated that the project would have an impact on the drinking and smoking habits of adolescents	United States
Brick *et al* [60], 2017 and Velicer *et al*[61], 2013	Grade 6, all genders	Yes	Yes	-	Multiattribute utility measurement approach	An intervention aimed at preventing substance use and promoting a healthy energy balance through physical activity, consumption of fruits and vegetables, and decreasing sedentary behavior	The outcome of every action was a significant decrease in the prevalence of smoking and drinking compared to the existing rates reported by ninth-grade students	United States
Werch *et al* [62], 2003	Grade 8, all genders	Yes	-	-	Randomized experimental design	Consultation for Sports (Sport): A process of evaluating one's health and fitness followed by discussion and recommendations	The program may boost the frequency of physical activity while decreasing alcohol consumption	United States
Goldberg *et al*[63], 2000	Grade 9 and grade 10, all genders	Yes	-	Yes	Randomized controlled trial	An education program centered on team collaboration and designed for a specific gender, which includes interactive classroom sessions and exercise training	The program was successful in stopping people from using alcohol and other prohibited drugs	United States
Butzer *et al* [64], 2017	Garde 7 (with a mean age of 12.64), all genders	-	Yes	-	Preliminary group randomized controlled trial	The curriculum of Kripalu Yoga in the Schools has a version that includes 32 sessions	Practicing yoga in schools can be helpful in reducing the inclination of both males and females towards smoking	United States
Fishbein *et al*[65], 2016	Grades 9 to 12 (mean age 12 yr), all genders	Yes	-	-	Pilot randomized controlled trial	A 20-session mindfulness yoga program created for students at risk of dropping out from school	The students who took part in yoga sessions showed a reduction in alcohol consumption	United States
Mathews *et al*[66], 2007	High school students, all genders	Yes	Yes	Yes	Randomized controlled trial	The project SPORT comprises of a brief interactive CD-ROM and a brief group consultation	The project received considerable acceptance among adolescent males and females and could be effective	United States
Horn *et al* [67], 2013	14-19 yr, all genders	-	Yes	-	Randomized group trial	The physical activity levels of participants in a smoking cessation program for teenagers improved with the addition of a physical activity component	Adolescents in good health are more likely to decrease their amount of smoking	United States

include integrating yoga into students' physical education classes to reduce their smoking habits[64,65] and combining exercise with an interactive CD-ROM to tailor exercise plans for students to execute independently[66]. The results of these studies confirm that exercise interventions are acceptable to adolescents and help reduce substance use behavior.

Table 4 Peer interventions and family-school cooperation

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Paquette *et al*[68], 2019	Ages 13-17, all genders	Yes	-	Yes	Randomized controlled trial	"Amplifying Our Futures (Amp)" is a temporary intervention program that consists of four phases. It is designed for adolescents who are at low to moderate risk of using substances and is facilitated by trained companions aged 18-28 years old	Young peer intervention was valuable in educational environments	United States
Botvin *et al*[69], 1990	Grade 7, all genders	Yes	Yes	Yes	Cluster randomized controlled trial	Life skills training is a program designed to improve cognitive and behavioral skills, which is led by both experienced students and teachers in a classroom setting for a total of 20 sessions	Preventative programs have had a quantifiable effect on behavior related to substance use	United States
Furr-Holden *et al*[70], 2004	Grades 1-8, all genders	Yes	Yes	Yes	Randomized prevention trial	The classroom-centered intervention and the family-school partnership intervention	Two interventions had a clear protective effect against tobacco use	United States
Zavela *et al*[71], 2004	Grades 4-8, all genders	Yes	Yes	Yes	Control experiments and follow-up questionnaire	Say Yes First-To Rural Youth and Family Alcohol/Drug Prevention: An educational and case management approach to drug prevention	The students who were part of the program consumed less alcohol, tobacco and other drugs and had a lower occurrence of marijuana use throughout their lifetime	United States
Winters *et al*[72], 2012	Ages 14-17, all genders	Yes	-	Yes	Randomized controlled trial	BIs: Therapists used the principle of motivational interviewing to conduct topical sessions with parents and students	BIs showed a connection with decreased drug usage, with a greater impact when parents were included	United States

Bis: Brief interventions.

Horn *et al*[67] combined physical activity and smoking cessation interventions for adolescents. The research suggested that students who increased their exercise time by 20 min were more likely to reduce their daily smoking quantity (Table 3).

Peer and family-school interventions: On the one hand, peer support is a protective factor for substance use problems in adolescents, and the role of peers can provide screening and intervention measures that are suitable for adolescent development[68]. Botvin *et al*[69] showed that peer intervention programs were more effective than regular classroom teaching. The Amplifying Our Futures program, jointly designed by multiple stakeholders such as schools, communities, and adolescents, is implemented by trained young adults. The results on the program confirmed the value of peers in substance use intervention in adolescents[68]. In addition, some research indicated that forming a partnership between families and schools, strengthening communication and exchange between the two parties, and effectively involving parents in adolescent substance use intervention can help reduce adolescents' early substance use behavior[70-72] (Table 4).

Electronic interventions: Currently, the application of electronic interventions in adolescent substance use is relatively limited. Examples include (1) Having teenagers watch videos and public service announcements[73] or teaching adolescents about alcohol, tobacco, and cannabis using electronic learning modules or programs[74,75]; (2) designing internet-based intervention plans for teenagers[76,77]; and (3) adopting alcohol media literacy programs to enhance teenagers' media literacy skills and reduce the potential impact of substance use-related advertisements on teenagers[78]. However, researchers have not yet reached a consensus on the effectiveness of electronic interventions. It is suggested that internet-based intervention plans are convenient for reducing alcohol and cannabis use, and research results showed that students in the intervention group reduced alcohol use one year after completing the course[76]. However, a web-based program called Consider This, implemented by Buller *et al*[77], was found to be of little value in preventing adolescent substance use (Table 5).

Differences in substance use intervention measures for adolescents at different educational stages

Adolescence is a critical period for preventing substance use. Through a literature review and summary, we found that intervention measures for substance use among adolescents at different educational stages need to focus on different

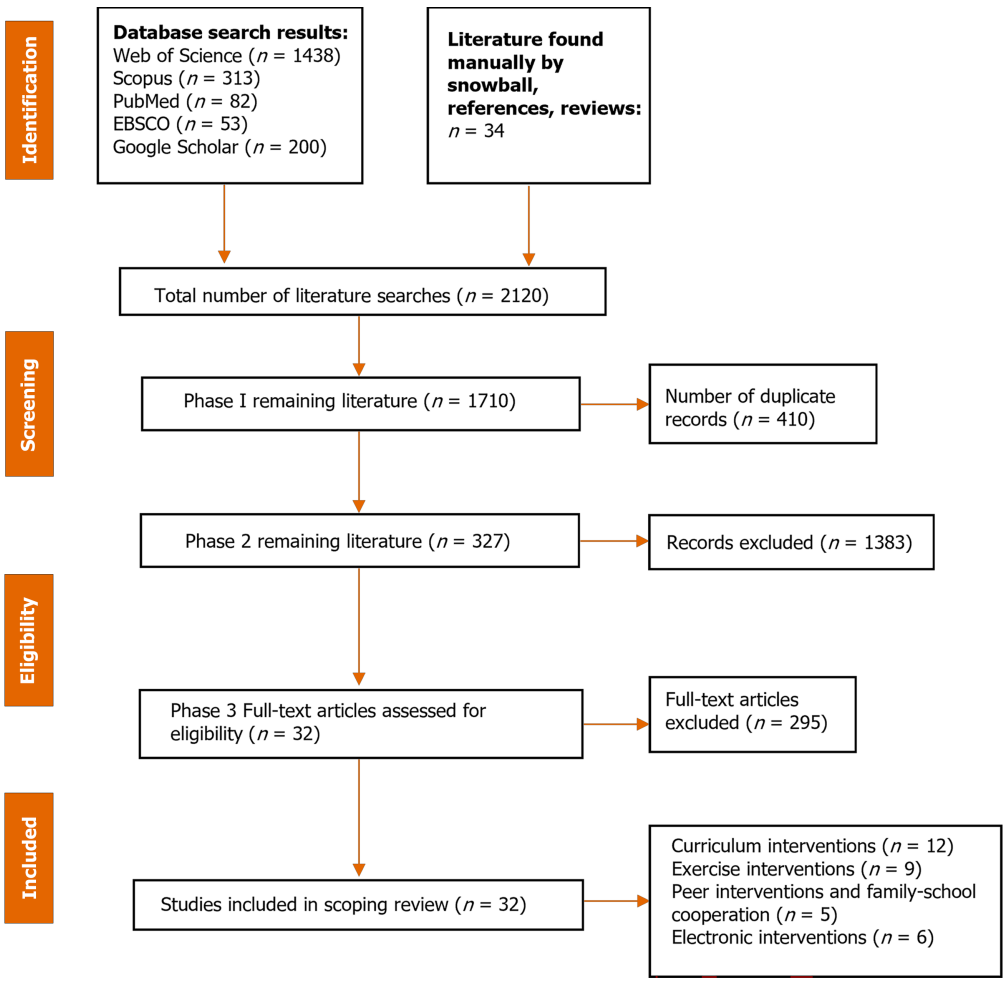
Table 5 Electronic interventions

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Jennifer *et al*[73], 2006	Grade 7, all genders	Yes	Yes	Yes, marijuana	Randomized controlled trial	The usefulness of the Drug Resistance Strategies Project's Keepin' it REAL program aimed at preventing adolescent substance use was explored by studying students who participated in it through public service announcements and videotapes	Class videos influenced the use of drugs among teenagers, whereas PSAs did not have an impact	United States
Malmberg *et al*[74], 2014	11-15 yr, all genders	Yes	Yes	Yes	Randomized clustered trial	Healthy School and Drugs program: Digital modules for e-learning and comprehensive intervention	Both the e-learning and comprehensive intervention failed to prevent the initiation of alcohol, tobacco, or marijuana use	The Netherlands
Kiewik *et al*[75], 2017	12-16 yr, all genders	Yes	Yes	-	Pre-/post-intervention pilot study with a control group	"Prepared on time": A digital training program that follows the attitude-social influence-efficacy model	This research demonstrated that an electronic learning prevention program is feasible for teenagers with mild or moderate intellectual disability	The Netherlands
Newton *et al*[76], 2010	13 yr, grade 8, all genders	Yes	-	Yes	Cluster-randomized controlled trial	Internet-based prevention programs for school-age children: The Climate Schools: Alcohol and Cannabis course	After finishing the programs, students' understanding of alcohol and cannabis improved, and it also led to a decrease in the consumption of alcohol for up to twelve months	Australian
Buller *et al* [77], 2008	Grades 6 to 9, all genders	-	Yes	-	Randomized trials	Consider This: There were a total of 73 online activities divided into six modules: Introduction, media literacy, relationships, mind and body, decision making, and resistance strategies	The activities led to a decrease in smoking and/or a decrease in students' expectations of smoking in the future	Australia and United States
Gordon *et al*[78], 2017	9-12 yr, all genders	Yes	-	-	Qualitative assessment	Alcohol media literacy programs: Providing children with the necessary skills to question and critically evaluate the information they receive from media sources	Using culturally specific advertisements as a means to educate about the effects of alcohol proved to be a potent strategy	Australia

areas. One demonstration project on minimizing drug harm confirmed this view. In this project, a quasi-experimental intervention was conducted with middle school and high school students for four years. The results showed that education on minimizing drug harm was not suitable for middle school students[79]. We believe that this may be related to the developmental characteristics of adolescents at different educational stages. Adolescents in the upper grades of primary school and in the junior high school stage are in a semimature state and are more prone to imitate behaviors such as smoking and drinking due to curiosity or a psychological desire for conformity. Therefore, at this stage, interventions should focus on guiding adolescents' behavior and values. High school students are relatively mature and have higher levels of cognition and behavioral abilities. Some students in this group may already have varying degrees of substance use disorders. Therefore, interventions should focus on consolidating awareness education and preventing increase substance use.

Advantages and challenges of substance use interventions for adolescents in educational environments

Advantages: Educational environments provide convenient spaces for intervening in substance use among adolescents. The advantages can be summarized in the following five aspects. First, school environments are the context of various interpersonal relationships, including those involving peers, teachers, and administrative personnel. Support from interpersonal relationships is a protective factor against adolescent substance use[80]. Intervention plans for the school context can combine the strengths of multiple stakeholders and maintain a high level of interaction among participants [73]. Examples include peer group pressure interventions[81] and family-school cooperation interventions[70]. Second, schools have unique advantages in terms of facilities and human resources. Evidence suggests that collective interventions are effective in treating adolescent mental health problems and substance use disorders[82]. Schools are



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Figure 1 Literature screening process.

ideal places to conduct collective interventions. Teachers can use the school's basic equipment and multimedia devices to conduct general courses to prevent substance use disorders, teach students about the potential risks of substance use, and enhance their decision-making and drug refusal abilities[82]. Third, many behaviors of adolescents, including substance use, are related to their experiences in school. Therefore, intervention plans for the school context can change the external environment to which adolescents are exposed and have external validity[72]. Fourth, it is easy to conduct large-scale screening for substance use in educational environments. Effective early screening for substance use problems is essential for preventing or delaying the use of alcohol, tobacco, and illegal drugs during the vulnerable period of adolescent substance use problems. Schools can use standard screening tools to screen students regularly and universally to identify potential substance use problems as early as possible and implement targeted interventions in a timely manner. Fifth, research shows that there may be a mechanism of mutual influence between students' mental health problems such as anxiety and depression and their substance use behaviors[6,7]. These problems are not conducive to the healthy growth and academic progress of adolescents. Schools provide a favorable environment for addressing these issues. Intervention measures in the school context can alleviate the substance use behavior of at-risk groups, promote the physical and mental health and academic performance of students, and create a virtuous circle, benefiting more adolescents.

Challenges: There is no doubt that education settings face many challenges in providing effective substance use interventions for adolescents. First, intervening with students who already have substance use disorders in schools can potentially compromise their privacy, leading to stigmatization risks. When students are afraid of being labeled as having "drug use problems" and refuse school intervention measures, the work becomes difficult[72]. Second, school-based intervention programs often require approval from the school board and coordination among multiple departments. However, considering the school's image, the board may deny the existence of substance use problems at different levels in the school to avoid affecting its enrollment and future development[83]. In addition, it is difficult for multiple departments to reach a consensus on the design and implementation of an intervention plan, and there may be complex problems such as misunderstandings and slow progress during the implementation process. Third, providing substance use-related courses for adolescents undoubtedly increases the burden and pressure on teachers and administrators, perhaps because they need to receive training from professionals in advance and spend much time and energy on teaching. Teachers and administrators also bear pressure from their own teaching tasks and other administrative work,

which may lead to role conflict and role overload[84]. Therefore, schools may need to provide necessary incentives for the implementers of intervention plans to increase their motivation. Fourth, the school environment increases the availability of alcohol, tobacco, and illegal drugs. In a 2009 study on adolescent risk behavior, 23% of students reported being offered drugs in school[82]. This indicates that in addition to actively formulating intervention plans, schools still need to build a positive, environmentally friendly, and healthy campus environment to prevent the spread of the use of alcohol, tobacco, and illegal drugs in schools. Fifth, as "digital natives", adolescents have a higher acceptance of electronic interventions than older age groups. However, the effectiveness of electronic interventions for adolescents with substance use disorders is not ideal. In the context of rapid informatization, fully tapping the potential of internet interventions and further introducing digital intervention in educational settings remains a challenge for school health workers and researchers.

DISCUSSION

In the face of the public health challenges posed by adolescent substance use and abuse, schools have an important mission as ideal places to implement intervention plans. In addition to carrying out regular substance use screening and implementing intervention plans according to different categories (such as universal intervention measures for all students, selective intervention measures for students at high risk of substance use, and directive intervention measures for students with substance use disorders), in the future, school-based intervention measures can focus on introducing big data and artificial intelligence technology; integrating advantageous resources from families, schools, and communities; and combining psychological health interventions.

Fully utilizing big data and artificial intelligence technology. In recent years, with the rapid development of artificial intelligence, machine learning, and deep learning, digital intervention methods have rapidly emerged. Schools can use artificial intelligence technology to build a platform for adolescent health management, establish a management mechanism that spans the full process from substance use screening warnings to intervention tracking, and enhance the coverage and accuracy of screening warnings. This platform can also incorporate the psychological health status of adolescents, thereby supporting the creation of personalized health records. In addition, precise assessment and prediction of student substance use problems and hierarchical classification intervention tracking through artificial intelligence technology can reduce the incidence of risky behavior. It is worth noting that when introducing digital intervention methods such as intelligent robots and applications, effectiveness and risk assessments should be conducted, operational procedures should be refined, and the potential of digital interventions should be truly realized.

Resources from families, schools, communities should be integrated to form joint efforts. When schools intervene in adolescent substance use problems, they need to consider protective factors from families, and students also need to recognize the importance of social influences. Currently, there are a variety of diverse intervention measures based on individual entities such as families, communities, and schools, and their effectiveness is significant; however, there is a lack of linkage between these entities. In the future, schools can encourage parents and communities to actively participate in the project while ensuring the integrity of their own intervention plans and managing and coordinating resources.

Psychological health interventions should be integrated, and comorbidity risks should be emphasized. Early substance use in adolescents is related to their psychological health status[85]. Identifying potential psychological health problems in adolescents and intervening in a timely manner can help reduce substance use risks[86]. Therefore, the early identification and intervention of both cannot be separated. When schools screen students for psychological health problems, they should pay attention to substance use, and when implementing substance use interventions, they should pay attention to potential psychological health problems in high-risk groups. This not only maximizes the use of school resources but also prevents adolescents from engaging in risky behavior due to comorbidities.

Furthermore, since this study is a scoping review, we did not calculate specific variable values, nor did we conduct a bias risk analysis. This is a limitation of this study.

CONCLUSION

This article outlines substance use prevention interventions for adolescents in educational environments and their implementation effects. We found that overall intervention measures include curriculum interventions focusing on cognitive-behavioral skill enhancement, exercise interventions, peer interventions and family-school collaboration, and electronic interventions. Except for electronic interventions, which have uneven implementation effects, intervention measures are beneficial in alleviating adolescent substance use problems to varying degrees. In addition, adolescents in different educational stages have different developmental characteristics, and intervention measures should be more targeted and focused. The educational environment has unique advantages for implementing intervention plans, and equipment and human resources can be used to provide adolescents with various types of intervention measures. However, implementation of interventions in the educational environment also faces challenges such as stigmatization, inadequate coordination among multiple resources, and poor implementation effects. In the future, school-based intervention measures can make full use of artificial intelligence technology, jointly intervene with families and communities, and pay attention to the comorbidity risks of substance use disorders and mental health issues.

FOOTNOTES

Author contributions: Liu XQ designed the study; Liu XQ, Guo YX, and Wang X wrote the manuscript and conducted the literature analyses; and all authors contributed equally to this work and approved the final manuscript.

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ORIGINAL ARTICLE

Case Control Study

Population-based affective-disorder-related biomedical/biophysical multi-hyper-morbidity across the lifespan: A 16-year population study

David R L Cawthorpe, Dan Cohen

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Abstract

BACKGROUND

There are few if any life-span population-based studies of psychiatric disorder-associated biomedical and biophysical disorders and diseases (morbidity).

AIM

To scope the present state of research regarding the biomedical and biophysical morbidity associated with affective and mental disorder in epidemiological samples, and to examine the life-span relationship between affective disorders and biomedical/biophysical disorders to illustrate a novel approach employing the odds ratio to represent the intensity of biomedical and biophysical morbidity associated in time in a population.

METHODS

A repeatable systematic literature search of PubMed was represented in summary. Additionally, a regional population-based dataset was constructed and analyzed to represent the age- and sex-specific diagnoses (International Classification of Diseases Version 9, ICD-9) for those with and without affective disorder. The analysis presents a novel index of the relative age-specific frequency of life-span biomedical and biophysical diagnoses associated with affective disorder.

RESULTS

The volume of biomedical and biophysical morbidity associated with mental disorder literature has increased, yet few studies measure comprehensive temporal hyper-morbidity (over-representation of diseases over time, either

before or after the index diagnostic event) in populations. Further, there have been only a few population-based studies examining the morbidity associated with affective disorder and only one that examines the full diagnostic range of lifespan morbidity. Substantial differences arose between males and females with more females than males having greater frequencies of diagnoses. The age-specific distributions of the maximum proportional diagnosis frequency ratios for each sex illustrate the greatest diagnosis-specific differences when comparing the biomedical and biophysical diagnoses of those with and without affective disorder when the same diagnosis was represented in each grouping at the same age.

CONCLUSION

Clinical research needs to focus on more than one or two comorbid biomedical or biophysical disorders at a time. Comprehensive population-based examination of the lifespan biomedical and biophysical multi-morbidity associated with affective disorder has the potential to directly inform clinical practice. Representing the proportional ratios of age-specific frequency of diagnoses for the full range of ICD-9 diagnoses is a novel analytical model. Diagnostic frequency appears a viable representation of a given disease state, such as affective disorder. Fortunately, the WPA has developed a global education section to better understand the biomedical and biophysical morbidity associated with all psychiatric disorders. This has been identified by the WPA as the psychiatric practice challenge of the 21st century.

Key Words: Biomedical/biophysical morbidity; Temporal hyper-morbidity; Mental disorder; Population; Epidemiology

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Core Tip: The paper presents a scoping review of publications with focus on the biomedical and biophysical morbidities associated with psychiatric disorder and a novel example from a population of the relationship between affective disorder and the frequency of associated biomedical and biophysical morbidities across the lifespan.

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INTRODUCTION

Numerous recent studies have examined the comorbidity of affective disorders and other mental processes[1-5] and disorders[6-9]. Less common is the study of biomedical or biophysical and affective disorder comorbidity. The studies that do address the comorbidity of affective disorders and biomedical diseases and disorders, predominantly focus on one singular biomedical diagnosis, such as diabetes[10-12] and chronic pain[13,14]. A few studies investigated a range of comorbid disorders, such as asthma, diabetes, epilepsy, food allergy, or juvenile arthritis arising within 6 mo of any mental problem[15]. In one study, biomedical markers have been identified indicating links between mental disorder and chronic physical illness[16]. Overall, the study of biomedical and biophysical morbidity in association with mental disorders has been constrained.

To date, while there have been some large sample studies of mental[17-20] and physical disorders[21-24], there have been few large sample studies examining relationship specifically between psychoses, such as affective disorders and biomedical/biophysical disorders. One large sample World Health Organization survey study found the number of medical conditions to increase with the number of psychotic symptoms within a 12 pre-survey month period[25]. In this study, a wide variety of medical conditions and health problems- such as angina, asthma, arthritis, tuberculosis, vision or hearing problems, mouth/teeth problems, alcohol consumption, smoking, and accidents - were reported to be more frequent in individuals with psychotic symptoms.

This altogether brief, focused, literature review outlines the constraints of studies focusing on psychiatric disorder-associated biomedical and biophysical morbidity. There is the need to introduce not only a broader perspective and definitions of morbidity, but also the need to find different approaches to its study.

The purpose of this study is twofold: First to present the current state of the art of biomedical and biophysical morbidity associated with mental disorder in large population-based samples in the published literature (PubMed). Secondly, both as an illustration and an example, we examined the lifespan association with affective psychoses of the full range of biomedical/biophysical diagnoses in a large 16-year regional population sample. We examined the full range of International Classification of Disease (ICD-9) biomedical and biophysical disorders and diseases in a population comparing those with affective disorder and those without any mental disorder. Further the paper presents a novel analysis and graphic representation of the frequency of biomedical and biophysical disorders and diseases of each specific ICD-9 disorder expressed as a ratio comparing the dependent groups.

The dataset in this study was originally compiled to investigate one *a priori* hypothesis in support of the original adverse childhood experience study[26-29]. The hypothesis assumed early adversity to be one gateway to subsequent mental disorder. Based on this assumption the hypothesis was that given the presence of any ICD-9 mental disorder diagnosis, biomedical and biophysical disorders would be proportionally greater than among those without any mental disorder. This proved to be the case with substantial over-representation of biomedical and biophysical disorders in those with any mental disorder[18].

The analysis underpinning the original study of this regional 16-year dataset was a relatively simple representation of the data in terms of odds ratios. Subsequently of interest was the temporal order of biomedical and biophysical disorders in relation to mental disorder and *vice versa*[20,22], in addition to the order of diagnoses in prospective age-defined cohorts[21,23].

MATERIALS AND METHODS

Literature search

Several PubMed searches of mesh and title terms provided an overview of the number of the current population-based psychiatric morbidity research publications (represented in tables associated with each searches' terms). Searching mesh and title terms provided an index of publication frequency with a focus on population, epidemiology, morbidity, and psychiatry. The details of each listed search result in PubMed recorded in Table 1 are repeatable. The results precisely list the total number of papers in each search. The position of the search (*e.g.*, title) indicates the importance of the terms in the search. In the results quotients are expressed in the terms of the results (number of publications) for the numerator expressed as a fraction of the results in generic search (unspecified position) for the denominator (#publications).

Cohort-study

The data for the population-based component of this study were collected under ethics ID REB15-1057. The data represented the health seeking population from the Calgary Health Zone in Alberta, Canada between April 1993 and November 2010. To receive payment all Alberta physicians, even practitioners in private clinics, directly bill the provincial health plan for each patient visit. The data consisted for each patient visit of a record that included an anonymous, encrypted, unique patient identifier, an ICD-9 diagnosis code, age, and sex. The analyzed data was grouped (dependent variable) according to the presence or absence of the ICD-9 diagnosis code 296 representing the affective disorders. The group wherein affective disorders were absent consisted of those without any mental disorders. The independent variable represented all biomedical and biophysical disorders linked within each group (+/- affective disorders). Additionally, the results were stratified on the variable age. The sexes were analyzed separately.

Analysis

The frequency of publications resulting from the PubMed literature searches were tabulated.

From the population-based based, the dependent groups were described in terms of age, sex, total frequency of diagnoses, counts of unique individuals together with the standard deviations and ranges.

The algorithm underpinning the comparative analysis of the groups with and without affective disorders ordered all diagnoses in sequence for individuals stratified by age within groups. Within each group for each diagnosis and each age, the total count of each diagnosis (frequency) was denominated by each age-specific sample size and represented as the proportion of the age-specific sample having a specific diagnosis in each group. For example, if each patient in each age-specific sample received one given diagnosis, the proportional value for that diagnosis would be one. If fewer than the total number of patients in each age-specific sample received a given diagnosis the proportional value would be less than one. If the age-specific sample received the diagnosis more than once each, then the proportional value would be greater than one. Novel in this analysis is the proportional value representing the intensity of any diagnosis within each age-specific strata of each dependent group.

Where age-specific diagnoses occurred in both dependent groups, between groups comparisons of the proportional diagnosis frequency ratio of each age-specific diagnosis for those with and without affective disorders was possible. While similar in formula construction to the odds ratio, the numerator of each group proportion represented each diagnosis' frequency (intensity) within the unique individuals at each specified age.

Ratio of Frequency Proportions of biomedical and biophysical disorders = [With/Without] affective disorder

The ratio of diagnosis frequency between the two groups, when greater than the value one, identifies that the intensity (frequency) of the diagnosis under comparison is greater in the dependent variable group with affective disorder. When the ratio of diagnosis frequency between the two groups is less than one, the diagnosis under comparison is greater in the dependent variable group without affective disorder. Diagnosis frequency within individuals is a way of representing the intensity of the associated disorders in the ratios of the compared groups.

Age-specific diagnoses could also occur in one group but not the other. Diagnoses that occurred only in one or the other group were noteworthy based on the possibility of conferring risk in the affective disorder groups or protection in the group without affective disorders. These diagnoses become asymptotic with the limit of value zero. Where a real frequency was greater in the group without affective disorder the value was between zero and one.

All ICD diagnoses were coded according to the numeric values of their natural codes, with V codes assigned values in the 1200 range and procedures (laboratory, anesthesiology, *etc.*) in the 1500 range.

Table 1 Volume of research publications for repeatable PubMed literature searches

Search condition	Frequency of results
"Consortium in Psychiatric Epidemiology"[Title]	0
"International Consortium in Psychiatric Epidemiology"[Title]	0
"International Consortium in Psychiatric Epidemiology"	6
"Psychiatric Epidemiology"[Title]	245
"ICPE" AND "psych*"	379
"ICPE" AND (psych*[Title])	60
morbid*[MeSH Terms] AND epidemiolog*[MeSH Terms] AND psych*[MeSH Terms]	165364
morbid*[MeSH Terms] AND epidemiolog*[MeSH Terms] AND mental[MeSH Terms]	0
((morbidity[MeSH Terms]) AND (epidemiology[MeSH Terms])) AND (psych*[MeSH Terms])	309
comorbidity[MeSH Terms] AND "epidemiology"[MeSH Terms] AND "psych*"[MeSH Terms]	56
"comorbidity"[Title] AND "epidemiology"[Title] AND "psych*"[Title]	18
((morbidity[Title]) AND (epidemiology[Title])) AND (population[Title])	12
((morbidity[Title]) AND (epidemiology[Title])) AND (psych*[Title])	10
((morbidity[Title]) AND (epidemiology[MeSH Terms])) AND (psych*[MeSH Terms])	8
"International Consortium in Psychiatric Epidemiology" - Articles found by citation matching	6
"morbidity"[Title] AND "epidemiology"[MeSH Terms] AND "psych*"[Title]	2
((morbidity[Title]) AND (epidemiology[Title])) AND (mental[Title])	1
(psych*) or (mental)	3347210

The representation of age-specific diagnoses provides an index of the frequency or intensity of occurrence over lifespan of the biomedical and biophysical diagnoses associated with affective disorder.

RESULTS

Literature Searches

Table 1 shows 17 searches. The last search represents all searchable fields of publications containing the wildcard psych@ and mental. The value of this search serves to denominate the largest value with the MeSH term search for the wildcard terms morbid*, epidemiolog*, and psych*. Of note the same search with mental replacing the wildcard term psych* produced zero results. The most generous quotient value indicates that 4.94% (165364/3347210) of the search research results had a precise focus on the MeSH terms. It may also be seen in Table 1 that when the MeSH terms are more precisely constrained (*e.g.*, morbidity, epidemiology, or comorbidity) there are substantially fewer results and even fewer when these terms are searched for in titles alone. Note that the PubMed graphic associated with the search resulting in 165364 articles showed that the articles per year peaked in 2019 with a total of 10239 articles published.

Population sample description

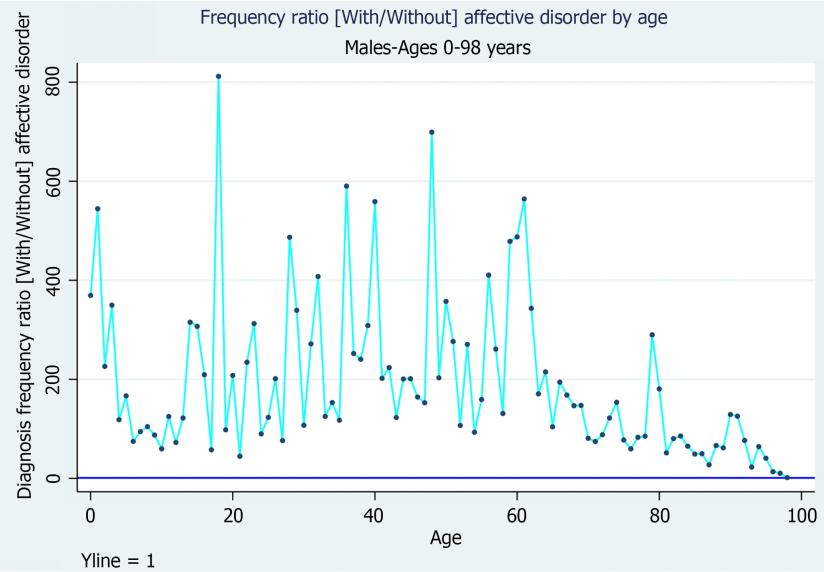
Table 2 describes the distributions of the groups with and without affective disorder. Note that the group without affective disorder consists of individuals without any other mental disorders. As well, there are more females than males with affective disorder and females have in total and on average a higher frequency of biomedical and biophysical diagnoses (mean = 291) compared to males (mean = 239). The average age of females is older than males in the group with affective disorder and younger in the group without affective disorder.

Note in the following graphs when the frequency of diagnosis ratios for each dependent group is equal to the value one, it means that the ratio of each group is equal. When greater than the value one, the ratio is greater in the group with affective disorders. When less than the value one, the ratio is greater in the group without affective disorders. Figure 1 shows the proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing males with and without affective disorder. Figure 2 shows the proportional frequency ratios > 1 distribution of maximum values comparing in males comparing those with and without affective disorder. Figure 3 shows the complete proportional ratios > 1 distribution comparing males with and without affective disorder. Figure 4 shows the proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing females with and without affective disorder. Figure 5 shows the proportional frequency ratios > 1 distribution of maximum values comparing in females comparing those with and without affective disorder.

Table 2 Demographics and diagnosis frequency of groups with and without affective disorder

Variables	Affective disorder	
Females	With	Without
Unique individuals	23637	141427
Mean age	47	38
SD age	20	24
Range age	(1-104)	(0-103)
Mean diagnoses	291	56
SD diagnoses	253	66
Range diagnoses	(1, 3164)	(1, 2424)
Total diagnoses	6881012	7986931
Males	With	Without
Unique individuals	16164	165527
Mean age	35	46
SD	23	19
Range age	(0, 103)	(0, 102)
Mean diagnoses	239	44
SD diagnoses	257	58
Range diagnoses	(1, 4316)	(1, 1864)
Total diagnoses	3862550	7301122

SD: Standard deviations.

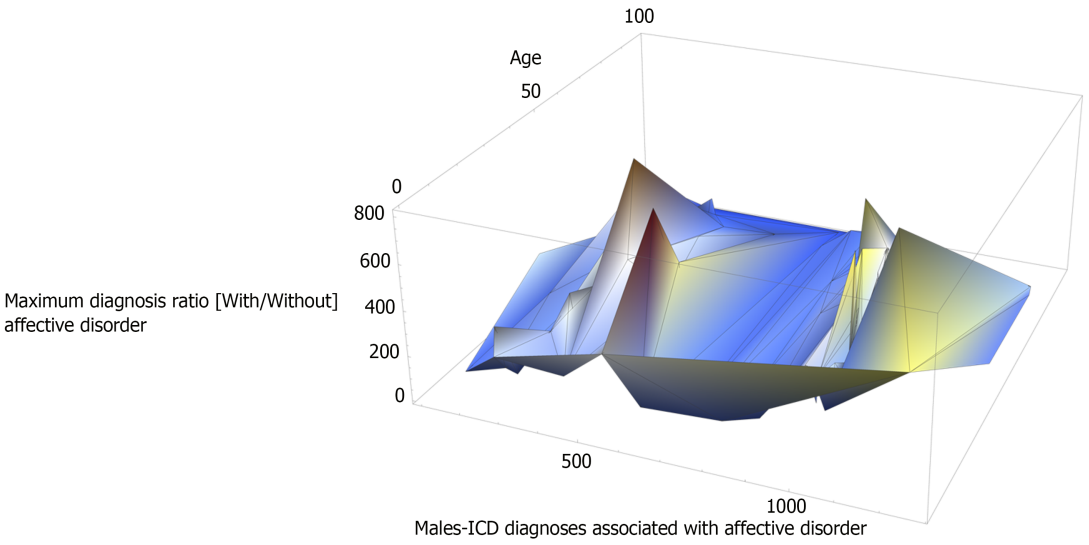


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Figure 1 Proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing males with and without affective disorder.

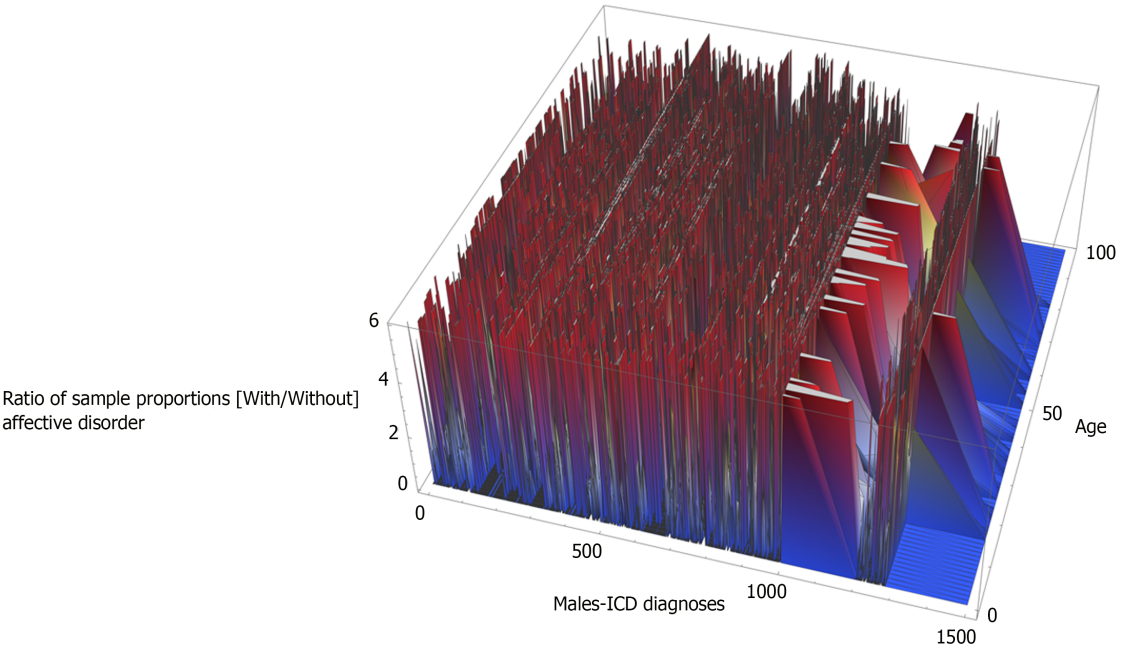
Figure 6 shows the complete proportional ratios > 1 distribution comparing females with and without affective disorder.

Overall, the reader might take away the following main points of the graphic representations of comparative unique frequency ratios of diagnosis for all ICD-9 diagnoses by age are as follow: (1) Those with affective disorder have greater frequencies of unique ICD-9 diagnoses across age; and (2) Males are substantially different than females.



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Figure 2 Proportional frequency ratios > 1 distribution of maximum values comparing in males comparing those with and without affective disorder.



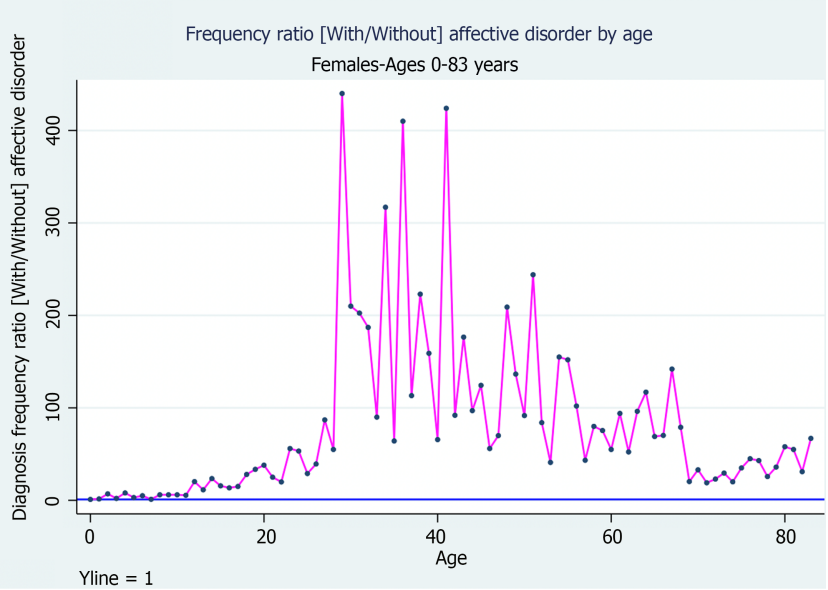
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Figure 3 Complete proportional ratios > 1 distribution comparing males with and without affective disorder.

In Figures 1 and 4, the maximum proportional diagnosis frequency ratios' distributions for males and females across all ages most clearly illustrate the sex differences. For example, the age-specific maximum proportional diagnosis frequency ratios are greater for males earlier in life. The maximal values in Figures 1 and 4 are greater than Figures 2 and 5 and more so in Figures 3 and 6, as the values in the latter figures are distributed across the frequency of individual diagnoses for a given sample size, rather than quotients within the summed frequency across the range of all ICD disorders within in a given age-specific sample sizes comparing the groups with and without affective disorder.

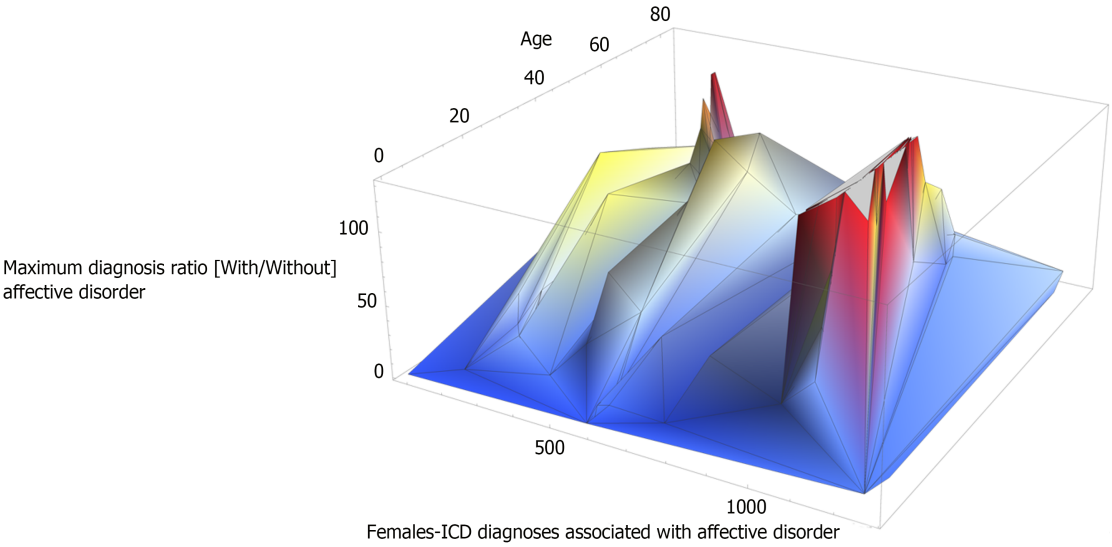
Figures 2 and 5 illustrate the sex differences within the subset of age-specific proportional diagnosis frequency ratios distributions for males and females showing the maximum proportional diagnosis frequency ratio values for each age across the full range of ICD diagnoses. Note that the graphs truncate around the proportional diagnosis frequency ratio less than 800 for males and about 100 for females, indicating a much higher proportional frequency of age-specific diagnosis for males.

From the full distribution of age-specific proportional diagnosis frequency ratios distributions shown for males and females in Figures 3 and 6, it is apparent that females have more laboratory testing and procedures, while males have



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Figure 4 Proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing females with and without affective disorder.



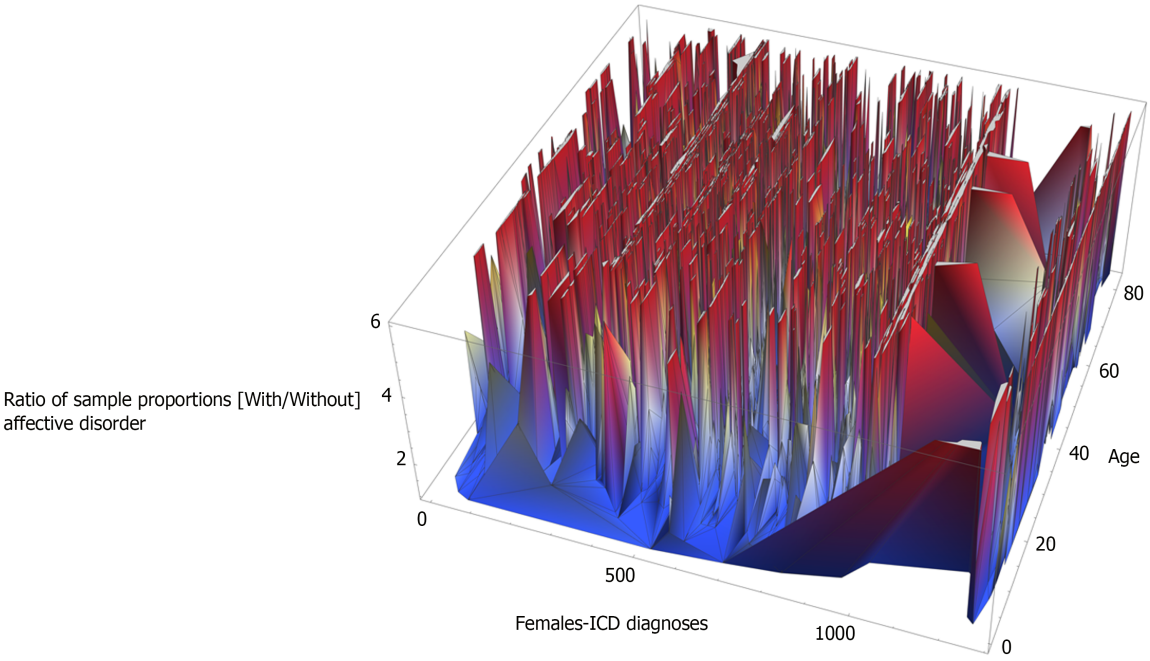
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Figure 5 Proportional frequency ratios > 1 distribution of maximum values comparing in females comparing those with and without affective disorder.

more V code diagnoses. Figures 3 and 6 both automatically truncate for visualization at the value 6.0 for both males and females when the full distributions are represented. The areas of the visible plateaus are relative to the height of each where the sequence of disorders by age reach their maximal peaks. Further, Figures 3 and 6 represent the ratios of the average frequency quotients for those with and without affective disorder, rather than the maximum values by age across all ICD disorders. Note the frequency of peaks closer at the value 1200 on the diagnosis axis comparing males and females, the frequency of V-Code peaks is greater for males across all ages. Similarly, note the frequency of peaks closer of the value 1500 on the diagnosis axis comparing males and females, the frequency of Laboratory Testing peaks is greater for females across all ages.

DISCUSSION

Our first purpose, examination of the volume of population-based morbidity literature, yields clear results. The PubMed search scope indicates that there has been a rapid increase in morbidity focused research after 1990 with a peak number of



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Figure 6 Complete proportional ratios > 1 distribution comparing females with and without affective disorder.

publications (n = 10238) in 2019. However, the specific publications cited in this paper indicate that only a minority (4.94%) specifically focus on mental disorder associated temporal biomedical and biophysical hyper-morbidity (Table 1). Even fewer account for the full range of morbidity in populations[18-24].

Our second purpose was the examination of affective disorder associated life-span multi-morbidity of biomedical and biophysical diagnoses in a 16-year population sample. Each age-specific grouping could enter or leave the dataset in any of the 16 years. Other studies of the same dataset focusing on prospective cohort samples (*e.g.*, < 1 year of age before January 1, 1995) in comparison to the same age group across the 16-year sample provide evidence indicating that all ages across the whole 16-year grouping in the current analysis does not unduly bias the results[23]. Thus, we are confident that the cumulative age specific results are similarly unbiased.

As expected, our results illustrate substantial differences between males and females: we found that more females than males were diagnosed with greater frequencies of diagnoses at different ages. This outcome is similar to epidemiological population based studies of affective disorder[30-33].

When comparing the same biomedical and biophysical diagnoses between the two groups at the same age, the age-specific distributions of the maximum proportional diagnosis frequency ratios for each sex showed the greatest diagnosis-specific differences between the two sexes.

Possibly of interest are the biomedical and biophysical diagnoses that do not overlap for males and females between the groups with and without affective disorder. The within group age-specific proportional distributions (not represented as between group ratios) of the non-overlapping diagnoses may in the affective disorder group represent diagnoses associated with increased etiological or sequelae risk over time. It may also be possible that non-overlapping diagnoses may in the group without affective disorder may represent protective diagnoses. These speculations, however, are well beyond the data limits of the present study, albeit such information as is presented may serve as a signpost for future research.

Strengths

Representing the full range of ICD-9 diagnoses as well as examining the proportional diagnosis frequency ratios of overlapping age-specific diagnoses is a novel data representation model. For example, the main difference in comparison to other formula, such as the odds ratio, is that the within-sample intensity of age-specific diagnoses may be represented and compared. The odds ratio generally counts unique individuals, and as such, features such as the frequency of given diagnoses are lost in the comparison. Diagnostic frequency may be an indicator of the severity or chronicity of a particular disease state.

Limitations

The PubMed searches were not thorough or reviewed in terms of content. The searches deviated from typical systematic reviews or meta-analyses. The searches employed a standardized approach only to illustrate the volume of morbidity-focused research.

While proportional diagnosis frequency ratios of overlapping age-specific diagnoses may be a novel form of life-span data representation, it is also important to consider the within group proportions of age-specific diagnoses. It was noted in the methods that when this value exceeded 1.0 the whole within sample had received the diagnosis. The proportional

diagnosis frequency ratios of overlapping age-specific diagnoses reported in this study were not limited to only those disorders having within group proportions greater than the value one. The main reason for this omission was to represent the proportional diagnosis frequency ratios available within the full range of ICD-9 diagnoses. Future work will address this limitation.

Finally, the foregoing novel analyses are a pointer to the complexity of any understanding of the temporal hyper-morbidity of affective disorders, save any mental disorder. For example, a next level of complexity in analysis requires the calculation of the conditional order of diagnoses within individuals. Conditional order is not simply the frequency of diagnoses for the dependent groups of individuals in time, (total of diagnoses on date 1, 2, 3…n) independent of the diagnosis that each individual experiences before or after any given diagnosis. The conditional sequence of diagnoses within individuals may reveal more information that is relevant to the etiology and prognosis of disorders arising before and after an index diagnosis of affective disorder.

CONCLUSION

The study of complex morbidity is emerging as a primary field of research[34] with multiple levels of definition[35]. Despite a rapid increase in morbidity focused research after 1990, a small minority of 4.94% specifically focus on mental disorder associated temporal biomedical and biophysical hyper-morbidity. The publications cited in this paper indicate only a few are focused on lifespan, biomedical and biophysical, population-based, temporal, hyper-morbidity[18-24]. The present study represents to the best of our knowledge the first comprehensive population-based examination of the lifespan biomedical and biophysical multi-morbidity that is associated with affective disorder. By employing a novel model of data representation, we were able to show the intensity of the affective disorder associated diagnoses. Based on the present results, a paradigm shift is required in terms of how in psychiatric and medical practice morbidity is conceptualized, defined, and studied[36,37]. An important step in re-defining morbidity is illustrated in the recent establishment of the World Psychiatric Association Comorbidity Section, wherein the study of morbidity is identified as central 21st century challenge for psychiatry[38,39].

ARTICLE HIGHLIGHTS

Research background

The latest series of publications based on “big-data” leading to this one, have also, in part, contributed to the formation and development of the World psychiatric Association Comorbidity Section.

Research motivation

This overall study was inspired by the Adverse childhood experiences (ACE) study. ACE are associated with lifespan morbidity and many leading causes of death in adulthood. The ACE study is a landmark research effort that investigated the relationship between childhood abuse and household dysfunction, and the leading causes of death in adulthood. The study found that individuals who experienced adverse childhood experiences such as physical, emotional, or sexual abuse, neglect, household dysfunction (*e.g.*, substance abuse, mental illness, incarceration, and divorce), are at higher risk for several chronic health conditions and premature death. The findings of the ACE study demonstrate the far-reaching impact that childhood experiences can have on adult health and well-being. The study's results highlight the importance of addressing childhood trauma and promoting healthy family environments to prevent chronic disease and improve overall health outcomes in adulthood.

Research objectives

To orient all divisions of medicine to the fact that big data has shown important lifespan links between mental disorder and biomedical and biophysical diseases, wherein mental disorder is fundamental linchpin in time, generally leading to hyper-morbidity and hyper-morbidity is a linchpin to mental disorder; and to develop algorithms identifying the precise (conditional) order for individuals and examining how these orders group may prove useful to both clinical practice and research into disease mechanism.

Research methods

We are now developing advanced algorithms for the reduction of data for representation. The example in this paper presents a novel approach to analysis based on the intensity or frequency of total and unique diagnoses by age for all individuals in a large population. In this paper, about 90 million diagnoses for about 0.75 million individuals are reduced to one graphic for each of males and females of age by frequency of diagnosis ratios for each of about 1000 ICD diagnoses.

Research results

It is apparent that there is greater temporal hyper-morbidity for those with affective disorder compared to those without any psychiatric diagnosis. When different publication results are compared, there are different disease vulnerabilities (*e.g.*, cancer and ulcerative colitis) related to different classes of psychiatric disorders and *vice versa*.

Research conclusions

Understanding temporal hyper-morbidity (and perhaps hypo-morbidity) is dependent on large population-based datasets. The results are fascinating in the sense that analyzing whole stable populations over time is more like accounting than statistical analysis and the results from the first population health index paper were intra-ocular (*e.g.*, over 50% of the population has a mental disorder over 16 years and over 3 times the biomedical and biophysical disorders.) This is in line with the World Psychiatry Association's identification of the 21st century's challenge is understanding and responding to mental disorder-related biomedical and biophysical morbidity.

Research perspectives

The conditional groupings are complex (as in the graphics of this paper), and like a classical 'road map' problem, and will likely depend on smart algorithms and artificial intelligence to unravel the clinical meaning for practice related to the next patient who walks through the door and mechanisms underlying groups such as autism, cancers, ulcerative colitis and viral pneumonia). The work to date is largely a signpost, pointing in a future direction. Even so, ChatGPT has already been directed to write several testable algorithms. As it stands, the population health index centered on mental disorder indeed represents an inflation-proof mechanism by which regions and nations may evaluate the cost/benefit impact of universal population-based prevention/promotion and early intervention investments and strategies.

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FOOTNOTES

Author contributions: Cawthorpe DRL collected the data, designed the study, and conducted the analysis and paper draft; Cohen D provided constructive critique, expertise, edited the draft; all authors have reviewed and approved the final version.

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STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Case Control Study

Glutamate decarboxylase 1 gene polymorphisms are associated with respiratory symptoms in panic disorder

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Abstract

BACKGROUND

Genetic factors play an important role in the pathogenesis of panic disorder (PD). However, the effect of genetic variants on PD remains controversial.

AIM

To evaluate the associations between *glutamate decarboxylase 1 (GAD1)* gene polymorphisms and PD risk and assess the effect of *GAD1* gene polymorphisms on the severity of clinical symptoms in PD.

METHODS

We recruited 230 PD patients and 224 healthy controls in this study. All participants were assessed for anxiety and panic symptom severity using the Hamilton Anxiety Rating Scale (HAM-A) and Panic Disorder Severity Scale (PDSS). *GAD1* gene polymorphisms (rs1978340 and rs3749034) were genotyped and assessed for allele frequencies.

RESULTS

There were no significant differences between cases and controls in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034). In addition, the effect of *GAD1* (rs1978340 and rs3749034) on PD severity was not significant. However, regarding respiratory symptoms, patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotype.

CONCLUSION
Here, we showed that the A/A genotype of *GAD1* rs1978340 was associated with increased severity of respiratory symptoms in patients with PD.

Key Words: Panic disorder; Gene polymorphisms; Respiratory symptoms; Allele frequencies; Pathogenesis; Chinese population

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Core Tip: The study found that the A/A genotype of *glutamate decarboxylase 1 (GAD1)* rs1978340 was associated with increased severity of respiratory symptoms in patients with panic disorder (PD). However, there were no significant differences between cases and controls in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034), and neither did *GAD1* (rs1978340 and rs3749034) have a significant effect on the severity of PD symptoms. These findings suggest that genetic factors may play a role in the pathogenesis of PD, particularly in respiratory symptoms, but further studies with larger sample sizes are needed to confirm these results.

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INTRODUCTION

Panic disorder (PD), the most common anxiety disorder, is characterized by recurrent and unexpected panic attacks and has an estimated 12-mo and lifetime prevalence rates of 2.4% and 3.8%, respectively[1,2]; the lifetime prevalence rate of panic attacks is 13.2%[3]. PD typically occurs in young adults, and women are more likely to be affected than men. However, the etiology of PD is multifactorial and complex, involving genetic, environmental, psychological and neurobiological factors[2,3]. Recent studies examining twins and family shows that the heritability of panic disorder is 30%-40%, suggesting strong evidence for a genetic etiology[4]. To date, genetic studies have reported several susceptibility genes for PD such as *neuropeptide Y*, *catechol-O-methyltransferase* and particularly 5-HT system-related genes[5,6]. For example, a previous study found that patients with PD were characterized by significantly higher frequencies of the LL genotype and L allele variant of the 5-HT transporter-linked promoter region (5-HTTLPR)[7]. However, few of these findings have been replicated by other researchers, and the pathogenesis of PD remains unclear[8-12]. Therefore, other candidate gene polymorphisms in PD should be explored.

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the mammalian brain, and abnormalities in the GABAergic system have long been implicated in the pathophysiology of PD[13-15]. For example, a significant decrease in *GABA* has been detected in the anterior cingulate and medial prefrontal cortices of patients with PD[16]. The *GAD1* gene encodes the 67-kDa glutamic acid decarboxylase isoform (GAD67) and is the rate-limiting enzyme responsible for GABA biosynthesis from glutamic acid. The *GAD1* gene might play an important role in the GABAergic system. A previous study found a significant effect of rs1978340 on cingulate cortex GABA concentrations[17]. In addition, previous studies have indicated that *GAD1* rs3749034 is associated with mRNA expression[18]. Therefore, *GAD1* may be an important candidate gene in PD. Incidentally, previous reports have suggested that the *GAD1* single nucleotide polymorphisms (SNPs) rs3749034 or rs1978340 are significantly related to several psychiatric disorders such as bipolar disorder[19], schizophrenia[20], attention-deficit/hyperactivity disorder[21], and heroin dependence[22]. For instance, the allelic or genotypic frequencies of the rs1978340 polymorphism in heroin addicts significantly differ from those in normal controls[23]. However, few studies have examined the relationship between *GAD1* and PD, particularly in Chinese populations.

Previous genetic and chromosomal studies have yielded inconsistent results. It is likely that most cases of PD have a complex genetic basis. In addition, current data suggest that the genetic architecture underlying PD is heterogeneous and differs among cases[24]. PD is accompanied by various symptoms, including palpitations, accelerated heart rate, dyspnea, sweating, and chest pain. These symptoms may be linked to distinct genetic mechanisms, and genetic polymorphisms have been speculated to be linked to the discrete symptoms of PD. Hence, to test the hypothesis that the GAD1 polymorphism could be associated with PD, we have conducted a case-control study comparing the frequency of these SNPs (rs1978340 and rs3749034) in PD patients and healthy controls. Additionally, we examined the relationship between the presence of PD symptoms and these polymorphisms.

MATERIALS AND METHODS

Participants

A total of 230 patients with PD were recruited as in- and outpatients at the Department of Psychosomatics, Sichuan Provincial People's Hospital, from July 2012 to January 2016. Patients were qualified based on the following criteria: A primary diagnosis of PD performed by professional psychiatrists according to the standardized structured clinical interview of the diagnostic and statistical manual of mental disorders, fourth edition axis I disorders (SCID-I)[25], and no episodes of other psychiatric disorders in the past or at present. Additionally, 224 healthy controls (HCs) among community volunteers were recruited for the study during the same period. SCID-I was also performed by a trained clinical psychiatrist, and the HCs had no history of any psychiatric disorder or major psychiatric condition in their first-degree relatives. All participants in this study were Han Chinese, aged 18–60 years. None of the patients had acute or chronic somatic disorders, head trauma, or neurological illnesses. The study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital [reference number: (2016) Ethics Review (29)]. All participants provided written informed consent before the initiation of study procedures.

Measures

PDSS: The 7-item PDSS was used to assess the severity of panic symptoms for all patients, and participants were instructed to rate each item from 0 to 4 based on the severity of each symptom, with possible responses ranging from "none" to "extremely severe"[26]. The scale was translated into Chinese by Xiong[27], and the PDSS-Chinese version had good internal consistency (Cronbach's alpha) with an overall score of (0.83).

Hamilton anxiety rating scale

The Hamilton anxiety rating scale (HAM-A) scale comprises 14 items (anxious mood, tension, fear, insomnia, cognitive function, depressed mood, somatic anxiety (muscular system), somatic anxiety (sensory system), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior at interview) with 5-level responses for each item, *i.e.*, scores 0, 1, 2, 3, and 4 indicating not present, mild, moderate, severe, and very severe, respectively[28]. A total score > 17 indicates mild anxiety symptoms; 18-24, mild-to-moderate anxiety symptoms; and 25-30, moderate-to-severe anxiety symptoms.

DNA extraction and SNP genotyping

For each participant, 3 mL of peripheral blood was collected in EDTA tubes. An automatic nucleic acid extractor (TGuide M16; Tiangen Biotech, Beijing, China) was used to extract genomic DNA. SNP genotyping was performed using an improved multiplex ligation detection reaction (iMLDR) technique developed by Genesky Bio-Tech (Shanghai, China). The multiplex polymerase chain reaction (PCR) reaction volume included 1 μL GC-I buffer (Takara Bio Inc., Shiga, Japan), 3.0 mmol/L Mg^{2+}, 0.3 mmol/L dNTP, 1 U HotStar Taq Polymerase (Qiagen, Hilden, Germany), 1 μL genomic DNA (5–10 ng/μL), and 1 μL Multiplex-PCR primer mix. The cycling program for PCR was 95 °C for 120 s, followed by 11 cycles of 94 °C for 20 s, 65 °C for 40 s, and 72 °C for 90 s, and each cycle decreased by 0.5 °C. The third step comprised 24 cycles at 94 °C for 20 s, 59 °C for 30 s, and finally, 72 °C for 2 min, and a hold at 4 °C. The PCR product was purified with 5 U SAP and 2 U Exonuclease I at 37 °C for 1 h and then inactivated at 75 °C for 15 min. The primer and probe information is provided in Supplementary Tables 1 and 2, respectively. The ligation reaction included 1 μL of 10× ligation buffer, 0.4 μL 3′ ligation primer (2 μM), 0.25 μL Tag DNA ligase, 6 μL ddH_2O mixture, 0.4 μL 5′ ligation primer (1 μM), and 2μL purified multiplex PCR product. The ligation cycling program comprised 38 cycles at 94 °C for 60 s, 56 °C for 4 min, and a hold at 4 °C. Sequencing was conducted in 0.5 μL 500 LIZ Size Standard, 0.5 μL ligation product, and 9 μL Hi-Di mixture (ABI3730XL; Applied Biosystems, Waltham, MA, United States). Raw data were analyzed using GeneMapper v4.1 software (Applied Biosystems). A random sample accounting for approximately 5% of the total DNA samples was directly sequenced using Big Dye-terminator version 3.1 and an ABI3730XL automated sequencer (Applied Biosystems) to confirm the iMLDR results.

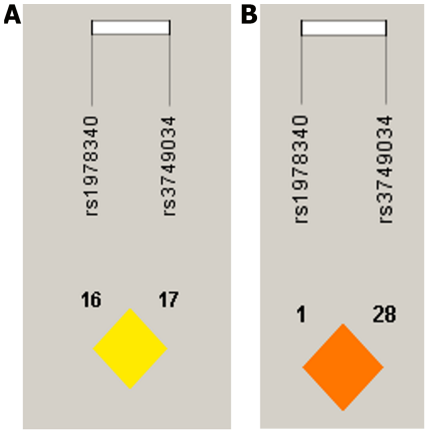
Statistical analysis

SPSS version 13.0 software (SPSS Inc., Chicago, IL, United States) was used to analyze the data. Student's *t*-test was used for intergroup comparisons of continuous variables, and Pearson's chi-square test was used for categorical variables. The Hardy-Weinberg equilibrium (HWE) *P* values were tested using Pearson's chi-square test. Associations between SNPs and PD were determined based on the distribution of allelic frequencies and genetic models (additive, dominant, and recessive models). Odds ratios and 95% confidence intervals were calculated by unconditional logistic regression analysis using PLINK v1.07. Analysis of variance was performed to compare the clinical variables with different *GAD1* SNPs (rs1978340 and rs3749034). Bonferroni's correction was used to avoid Type I errors. For all analyses, statistical tests were two-tailed, and an alpha level of 0.05 was used to define statistical significance.

RESULTS

Demographic data and clinical manifestations

The analyzed sample comprised 230 PD cases (92 men and 138 women; mean age, 35.38 ± 9.55 years) and 224 controls (100 men and 124 women; mean age, 36.57 ± 8.43 years). Of these patients, 54% (n = 124) resided in urban locations, and



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Figure 1 Linkage disequilibrium in *glutamate decarboxylase 1* polymorphisms (rs1978340 and rs3749034). A: Data from this study; B: Data from 1000 genomes.

46% (n = 106) resided in rural locations. No statistically significant differences were found between the cases and controls in terms of sex, age, or residential location (P > 0.05). For the PD patients, the mean course of PD was 2.80 ± 1.68 years, the mean PDSS score was 14.13 ± 3.74, and the mean HAM-A score was 22.07 ± 6.86 (Table 1).

Association of GAD1 (rs1978340 and rs3749034) polymorphisms with PD risk

HWE was measured in all genotyped individuals. *GAD1* (rs1978340 and rs3749034) polymorphisms fulfilled the HWE (P > 0.05) in both patients and HCs. The linkage disequilibrium evaluated in patients with PD and HCs for variants rs1978340 and rs3749034 of *GAD1* is shown in Figure 1 (R^2 > 0.9). The genotype and allele distributions of *GAD1* (rs1978340 and rs3749034) did not significantly differ between PD patients and HCs (P > 0.05) (Table 2).

Association of GAD1 (rs1978340 and rs3749034) polymorphisms with clinical manifestations in PD patients

There were no statistically significant differences in the total PDSS and sub-item scores among the three genotype groups of *GAD1* polymorphisms (rs1978340 and rs3749034; all P > 0.05) (Table 3).

However, there was a significant difference among the three groups with different *GAD1* rs1978340 genotypes in item 10 of the HAM-A score for PD (P < 0.01). In addition, post hoc analyses indicated that patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotypes (all P < 0.001), and the results remained significant after Bonferroni's multiple comparison adjustment (P < 0.01), reflecting a higher score for respiratory symptoms in patients with the *GAD1* rs1978340 A/A genotype than in those with the A/G or G/G genotype. However, there was no statistically significant difference among the three groups with different *GAD1* rs1978340 genotypes for the remaining items or HAM-A total scores (P > 0.05). Moreover, there was no significant association between *GAD1* rs3749034 and anxiety severity in PD patients (all P > 0.05) (Table 4).

DISCUSSION

In this study, regarding respiratory symptoms, which include chest tightness, choking, and breathing difficulty, we found that patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotypes. In other words, the present study showed that the *GAD1* rs1978340 A/A genotype was associated with increased severity of respiratory symptoms in patients with PD and demonstrated that the *GAD1* genotype might be related to symptomatic profiles rather than vulnerability to developing PD. In addition, our findings imply that different clinical features in PD patients are closely related to the heterogeneity of heredity. Compared with PD patients of the non-respiratory subtype (non-RS), previous studies have shown that patients with the RS subtype have a more extensive family history of PD[29]. Moreover, experimental animal research has provided evidence of the important role of GABAergic neurotransmission in the amygdala in modulating anxiety-related behaviors. For example, diminished GAD67 expression in the amygdala blunts the anxiolytic-like effects of diazepam in adult mice[30]. Furthermore, *GAD1* SNP rs1978340 is potentially functional because it affects GABA concentrations in the cingulate cortex[22]. In addition, the presence of *GAD1* rs1978340 allele A has been associated with a higher Glu/GABA ratio[31]. Clinical trials have shown that patients with PD and RS have a more rapid response to antidepressants and benzodiazepines than that of non-RS PD patients[32]. These findings contribute to our understanding of the mechanism linking *GAD1* rs1978340 with respiratory-related symptoms.

Similar findings suggest that patients with PD carrying the 5-HTTLPR s-allele experience the most severe panic and depressive symptoms[33]. Another study showed higher anxiety levels among A/G carriers than those among A/A carriers in patients[34]. It is evident that molecular genetics showed inconsistent results across different studies. This may be due to different sample sizes and ethnic differences. In addition, different clinical symptoms may be partly attributed

Table 1 Demographic and clinical characteristics in patients with panic disorder and controls, *n* (%)

Variable	PD (*n* = 230)	Controls (*n* = 224)	t/χ^2	*P* value
Sex				
Male	92 (40.0)	100 (44.6)	1.002	0.317
Female	138 (60.0)	124 (55.4)		
Age, yr	35.38 ± 9.55	36.57 ± 8.43	1.410	0.159
Educational level				
< Junior high school	49 (21.3)	43 (19.2)		
High school	95 (41.3)	92 (41.1)	0.412	0.814
College and above	86 (37.4)	89 (39.7)		
Resident location				
Urban	124 (53.9)	126 (56.3)		
Rural	106 (46.1)	98 (43.7)	0.250	0.617
Total duration of PD, yr	2.80 ± 1.68			
PDSS score	14.13 ± 3.74			
HAMA score	22.07 ± 6.86			

PDSS: Panic Disorder Severity Scale; HAMA: Hamilton Anxiety Rating Scale; PD: Panic disorder.

Table 2 *Glutamate decarboxylase 1* gene polymorphisms of patients with panic disorder *vs* controls in the Chinese population, *n* (%)

SNP	Alleles and genotypes	PD (*n* = 230)	Controls (*n* = 224)	Model	OR (95%CI)	*P* value
rs1978340	A	122 (26.5)	116 (25.9)	Allele[a]	1.003 (0.769-1.389)	0.829
	G	338 (73.5)	332 (74.1)			
	A/A	17 (7.4)	20 (8.9)	Additive[b]	1.031 (0.774-1.373)	0.835
	A/G	88 (38.3)	76 (34.8)	Dominant[b]	1.120 (0.773-1.622)	0.549
	G/G	125 (54.3)	128 (57.1)	Recessive[b]	0.814 (0.415-1.598)	0.550
rs3749034	A	131 (28.5)	129 (28.8)	Allele	0.985 (0.738-1.313)	0.916
	G	329 (71.5)	319 (71.2)			
	A/A	17 (7.4)	15 (6.7)	Additive	0.984 (0.732-1.323)	0.914
	A/G	97 (42.2)	99 (44.2)	Dominant	0.948 (0.656-1.370)	0.777
	G/G	116 (50.4)	110 (49.1)	Recessive	1.112 (0.541-2.286)	0.773

[a]Chi-square test.

[b]Logistic regression analyses.

OR: Odds ratios; CI: Confidence interval; SNP: Single Nucleotide Polymorphism, "A" represent wild type and "a" represent mutant type: allele, a *vs* A; additive, aa *vs* Aa *vs* AA; dominant, aa + Aa *vs* AA, recessive, aa *vs* Aa +AA; PD: Panic disorder.

to different genetic backgrounds, leading to difficulties in reaching a consensus on the etiology of PD. Further studies with larger populations are needed to obtain precise results based on different symptom subtypes.

In this case-control study, we examined two SNPs (rs1978340 and rs3749034) in a Chinese population. The results revealed that there was no association between *GAD1* and PD. In addition, we did not observe a modulatory effect of *GAD1* (rs1978340 and rs3749034) on PD severity. Much evidence has indicated that *GAD1* gene polymorphisms may be involved in the etiology of several psychiatric disorders. However, only one study has found that *GAD1* variation is associated with PD in females[35]. The different results of these studies might be partly attributable to differences in sample size and sex. Moreover, samples from different ethnicities and meta-analyses are required to further test this association. The SNP coverage in the present study was limited, and other gene polymorphisms should be considered. In addition, the pathogenesis of PD may involve the interaction of multiple genes and signal pathway regulation, which may incorporate the combined effects of genetic and environmental factors. For example, a previous study suggested the effect of the interaction between 5-HTTLPR and separate life events on PD[36]. Finally, epigenetic mechanisms have been

Table 3 Panic disorder severity scale subdimension scores of panic disorder with different *glutamate decarboxylase 1* rs1978340 and rs3749034 polymorphisms

Variable	rs1978340			*F*	*P* value	rs3749034			*F*	*P* value
	A/A (*n* = 17)	A/G (*n* = 88)	G/G (*n* = 125)			A/A (*n* = 17)	A/G (*n* = 97)	G/G (*n* = 116)		
PDSS1	2.12 ± 0.93	2.11 ± 1.09	2.14 ± 1.08	0.022	0.978	1.94 ± 0.97	2.06 ± 1.04	2.22 ± 1.10	0.837	0.434
PDSS2	2.41 ± 1.00	2.32 ± 1.00	2.44 ± 1.10	0.349	0.706	2.35 ± 1.41	2.28 ± 1.07	2.49 ± 0.97	1.099	0.335
PDSS3	2.41 ± 1.18	2.08 ± 0.89	2.14 ± 1.05	0.786	0.457	2.18 ± 1.13	1.99 ± 1.00	2.26 ± 0.98	1.934	0.147
PDSS4	1.59 ± 1.28	1.57 ± 1.04	1.66 ± 1.06	0.218	0.804	1.41 ± 1.12	1.76 ± 1.12	1.53 ± 1.00	1.590	0.206
PDSS5	1.71 ± 1.26	1.91 ± 1.01	1.76 ± 1.10	0.581	0.560	2.12 ± 1.22	1.67 ± 0.93	1.89 ± 1.63	1.818	0.165
PDSS6	2.33 ± 1.22	2.15 ± 0.97	2.11 ± 1.03	0.417	0.660	2.18 ± 1.33	2.09 ± 1.03	2.18 ± 0.97	0.206	0.814
PDSS7	1.59 ± 0.94	1.83 ± 1.01	1.97 ± 1.18	1.087	0.339	2.00 ± 1.06	1.85 ± 1.05	1.91 ± 1.15	0.174	0.841
PDSS total	14.18 ± 4.68	13.97 ± 3.39	14.23 ± 3.86	0.132	0.877	14.18 ± 4.99	13.70 ± 3.54	14.47 ± 3.69	1.134	0.323

PDSS1: Panic attack frequency, PDSS2: Panic distress, PDSS3: Severity of anticipatory anxiety, PDSS4: Agoraphobic fear/avoidance, PDSS5: Fear/avoidance of panic-related sensations, PDSS6: Work impairment, PDSS7: Social impairment, PDSS: Panic Disorder Severity Scale.

Table 4 Hamilton Anxiety Rating Scale subdimension scores of panic disorder with different *glutamate decarboxylase 1* rs1978340 and rs3749034 polymorphisms

Variable	rs1978340			*F*	*P* value	rs3749034			*F*	*P* value
	A/A (*n* = 17)	A/G (*n* = 88)	G/G (*n* = 125)			A/A (*n* = 17)	A/G (*n* = 97)	G/G (*n* = 116)		
HAMA1	1.59 ± 1.06	1.88 ± 1.16	1.81 ± 1.18	0.439	0.645	1.82 ± 1.33	1.81 ± 1.14	1.82 ± 1.17	0.001	0.999
HAMA2	2.00 ± 1.00	2.06 ± 0.94	2.17 ± 1.11	0.402	0.669	2.24 ± 1.30	2.07 ± 1.01	2.13 ± 1.03	0.206	0.814
HAMA3	1.94 ± 1.09	1.66 ± 1.07	1.98 ± 1.08	2.295	0.103	2.24 ± 1.25	1.78 ± 1.01	1.85 ± 1.11	1.260	0.286
HAMA4	1.71 ± 1.11	1.43 ± 1.11	1.58 ± 1.02	0.728	0.484	1.47 ± 0.87	1.48 ± 1.02	1.58 ± 1.12	0.231	0.794
HAMA5	1.59 ± 1.06	1.58 ± 1.04	1.65 ± 1.03	0.121	0.886	1.65 ± 1.17	1.55 ± 1.06	1.67 ± 0.99	0.402	0.670
HAMA6	1.53 ± 1.01	1.25 ± 1.05	1.54 ± 0.99	2.255	0.107	1.65 ± 1.32	1.38 ± 1.07	1.44 ± 0.94	0.498	0.747
HAMA7	1.76 ± 1.03	1.34 ± 0.99	1.62 ± 1.01	2.459	0.088	1.59 ± 1.06	1.46 ± 1.01	1.56 ± 1.02	0.277	0.759
HAMA8	1.06 ± 0.83	1.38 ± 1.10	1.37 ± 1.12	0.644	0.526	1.41 ± 0.94	1.34 ± 1.10	1.34 ± 1.11	0.032	0.969
HAMA9	2.06 ± 1.20	1.91 ± 0.99	1.94 ± 1.03	0.154	0.858	1.82 ± 1.13	2.08 ± 1.07	1.84 ± 0.97	1.647	0.195
HAMA10	2.88 ± 0.93	1.94 ± 0.98	1.90 ± 1.02	7.445	0.001	2.41 ± 1.00	1.94 ± 0.96	1.97 ± 1.08	1.601	0.204
HAMA11	0.76 ± 0.66	0.86 ± 0.79	0.97 ± 0.91	0.672	0.512	1.00 ± 0.94	0.89 ± 0.87	0.92 ± 0.82	0.143	0.867
HAMA12	1.00 ± 1.00	1.20 ± 0.96	1.34 ± 0.92	1.214	0.299	1.41 ± 1.00	1.22 ± 0.93	1.28 ± 0.95	0.340	0.712
HAMA13	1.12 ± 0.93	1.35 ± 0.87	1.30 ± 1.03	0.427	0.653	1.29 ± 1.11	1.25 ± 0.99	1.36 ± 0.92	0.377	0.687
HAMA14	1.59 ± 1.06	1.48 ± 0.98	1.35 ± 0.98	0.693	0.501	1.53 ± 1.28	1.44 ± 0.99	1.38 ± 0.94	0.229	0.796
HAMA total	22.59 ± 5.22	21.34 ± 6.94	22.50 ± 6.97	0.799	0.451	23.53 ± 7.13	21.70 ± 6.93	22.16 ± 6.75	0.535	0.587

HAMA1: Anxious mood; HAMA2: Tension; HAMA3: Fears; HAMA4: Insomnia; HAMA5: Intellectual; HAMA6: Depressed mood; HAMA7: Somatic complaints muscular; HAMA8: Somatic complaints sensory; HAMA9: Cardiovascular symptoms; HAMA10: Respiratory symptoms; HAMA11: Gastrointestinal symptoms; HAMA12: Genitourinary symptoms; HAMA13: Autonomic symptoms; HAMA14: Behavior at interview; HAMA: Hamilton Anxiety Rating Scale.

suggested to play important roles at the intersection of genetic and environmental factors[37]. Environmental factors may influence biological processes through epigenetic mechanisms, particularly DNA methylation[38]. For instance, patients with PD exhibit significantly lower average *GAD1* methylation levels than those of HCs[39]. Another study showed that patients had significantly lower methylation of the *GAD1* promoter region on cytosine-phosphate-guanine 7 than that of HCs, and a significant negative association was found between the cg171674146 site and clinical severity[40]. Therefore,

epigenetic modifications may play an important role and should be further investigated in future studies.

CONCLUSION

In conclusion, the present study showed that the A/A genotype of GAD1 rs1978340 is associated with increased severity of respiratory symptoms in patients with PD. However, the results of our study should be considered in light of the following limitations: Since this was a small sample investigating the associations between *GAD1* gene polymorphisms and PD, it would be valuable to replicate our findings in a larger cohort. In addition, SNP coverage in the present study was limited, and other gene polymorphisms should be considered.

ARTICLE HIGHLIGHTS

Research background

Genetic factors are known to play a significant role in the development of panic disorder (PD). However, the impact of genetic variants on PD is still a subject of controversy.

Research motivation

γ-Aminobutyric acid (GABA) is an important neurotransmitter that inhibits brain activity. Previous reports have linked the *glutamate decarboxylase 1 (GAD1)* genetic variants to various psychiatric disorders, including bipolar disorder, schizophrenia, attention-deficit/hyperactivity disorder, and heroin dependence. However, few studies have examined the relationship between *GAD1* and PD, particularly in Chinese populations.

Research objectives

The main objectives of this study were to examine the associations between *GAD1* gene polymorphisms (rs1978340 and rs3749034) and PD risk, and to determine the effect of these polymorphisms on the severity of clinical symptoms, specifically respiratory symptoms, in individuals with PD.

Research methods

The study included a total of 230 PD patients and 224 healthy controls. All participants underwent assessments for anxiety and panic symptom severity using the Hamilton Anxiety Rating Scale (HAM-A) and Panic Disorder Severity Scale (PDSS). The GAD1 gene polymorphisms (rs1978340 and rs3749034) were genotyped, and allele frequencies were analyzed.

Research results

The study findings revealed no significant differences in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034) between the PD cases and the control group. Furthermore, the *GAD1* gene polymorphisms (rs1978340 and rs3749034) did not exhibit a significant effect on the overall severity of PD. However, in relation to respiratory symptoms, PD patients with the *GAD*1 rs1978340 A/A genotype demonstrated significantly higher scores compared to those with the A/G or G/G genotype.

Research conclusions

In conclusion, this study demonstrated that the A/A genotype of *GAD1* rs1978340 is associated with increased severity of respiratory symptoms in individuals with PD. However, no significant associations were found between *GAD1* gene polymorphisms and the risk of developing PD or the overall severity of the disorder.

Research perspectives

Further research is needed to explore other potential genetic factors involved in the development and severity of PD. Additionally, investigating the underlying mechanisms through which *GAD1* gene polymorphisms affect respiratory symptoms in PD patients could provide valuable insights for future studies.

FOOTNOTES

Author contributions: Zou ZL contributed to study design, manuscript preparation; Qiu J contributed to experiment performance and data collection; Zhou XB, Huang YL, Wang JY contributed to data collection, analysis and inspection; Zhou B contributed to fund acquisition; Zhang Y contributed to manuscript preparation, inspection and revision.

Institutional review board statement: The study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital [reference number: (2016) Ethics Review (29)]. All participants provided written informed consent before the initiation of study procedures.

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ORIGINAL ARTICLE

Retrospective Study

Effects of health concept model-based detailed behavioral care on mood and quality of life in elderly patients with chronic heart failure

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Abstract

BACKGROUND

With the intensification of social aging, the susceptibility of the elderly population to diseases has attracted increasing attention, especially chronic heart failure (CHF) that accounts for a large proportion of the elderly.

AIM

To evaluate the application value of health concept model-based detailed behavioral care in elderly patients with CHF.

METHODS

This study recruited 116 elderly CHF patients admitted from October 2018 to October 2020 and grouped them according to the nursing care that they received. The elderly patients who underwent health concept model-based detailed behavioral care were included in a study group (SG; n = 62), and those who underwent routine detailed behavioral nursing intervention were included as a control group (CG; n = 54). Patients' negative emotions (NEs), quality of life (QoL), and nutritional status were assessed using the self-rating anxiety/depression scale (SAS/SDS), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the Modified Quantitative Subjective Global Assessment (MQSGA) of nutrition, respectively. Differences in rehabilitation efficiency, NEs, cardiac function (CF) indexes, nutritional status, QoL, and nursing satisfaction were comparatively analyzed.

RESULTS

A higher response rate was recorded in the SG *vs* the CG after intervention (P < 0.05). After care, the left ventricular ejection fraction was higher while the left ventricular end-diastolic dimension and left ventricular end systolic diameter were lower in the SG compared with the CG (P < 0.05). The post-intervention SAS

and SDS scores, as well as MQSGA and MLHFQ scores, were also lower in the SG ($P < 0.05$). The SG was also superior to the CG in the overall nursing satisfaction rate ($P < 0.05$).

CONCLUSION

Health concept model-based detailed behavioral care has high application value in the nursing care of elderly CHF patients, and it can not only effectively enhance rehabilitation efficiency, but also mitigate patients' NEs and improve their CF and QoL.

Key Words: Chronic heart failure; Elderly patients; Health concept model; Detailed behavioral care; Patient mood; Quality of life; Nursing effect

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Core Tip: Elderly patients with chronic heart failure (CHF) are prone to negative emotions (NEs) such as depression and anxiety during treatment. Although some drugs can alleviate NEs, they are not conducive to the cardiac function of patients. Therefore, effective means should be explored clinically to improve the mood and quality of life of elderly patients with CHF.

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INTRODUCTION

Chronic heart failure (CHF) is a clinically common cardiovascular disorder that may cause various complications[1,2]. The disease is difficult to treat with a high death rate, re-hospitalization rate, and bleak prognosis, resulting in great clinical attention to its treatment and nursing care[3]. In the current aging society, CHF patients account for a large proportion of the elderly population[4]. CHF in the elderly is characterized by a long course, multiple underlying comorbidities, and declined self-care ability, bringing huge economic burden to patients' families and society[5]. Elderly CHF patients are also predisposed to negative emotions (NEs) due to their age and unpredictable conditions[6]. Although drugs such as duloxetine can be used to relieve depression and other NEs, they may be disadvantageous to patients' cardiac function (CF)[7,8]. Effective nursing intervention is therefore extremely necessary, which is the key to improving patients' quality of life (QoL) and disease prognosis[9].

Conventional nursing intervention, being single and inflexible, cannot meet the actual needs of elderly CHF patients [10]. Health concept model-based detailed behavioral care, on the other hand, formulates nursing intervention programs through behavioral and social psychology, which encourages patients to take the initiative to adopt healthy behaviors, thus improving the treatment effect[11]. In addition, there is a positive correlation between health beliefs and healthy behaviors. Establishing correct health beliefs allows people to accept persuasion, change unhealthy behaviors, and actively adopt healthy behaviors[12]. At present, the health belief model has been widely used in the health education of various diseases with good effects achieved[13]. Besides, chronic and unremitting symptoms and long treatment process significantly reduces the QoL of CHF patients while causing NEs such as anxiety and depression[14]. Health education can mitigate the NEs of elderly CHF patients and enhance their disease awareness to mitigate their fear of the disease due to insufficient awareness[15].

Based on the above, this study explored the application value of health concept model-based detailed behavioral care in the care of elderly CHF patients.

MATERIALS AND METHODS

Patient information

The clinical data of 116 elderly patients with CHF admitted to the Affiliated Hangzhou First People's Hospital Zhejiang University School of Medicine from October 2018 to October 2020 were analyzed retrospectively. Patients who underwent health concept model-based detailed behavioral care were included in a study group (SG; $n = 62$, male-female ratio 40:22) and those who underwent routine detailed behavioral nursing intervention were included in a control group (CG; $n = 54$, male-female ratio 29:25).

Eligibility criteria

The enrolled patients all were aged ≥ 60 years, with a confirmed diagnosis of CHF[16], complete clinical data, and active cooperation with treatment. Patients and their families were informed and consented to participate in the study.

Patients with chronic obstructive pulmonary disease, cerebral toxicosis, hyperthyroidism, inability to eat normally, cognitive and consciousness disorders, serious infections, malignant diseases, and limited mobility or those who were otherwise unable to complete all care measures were excluded from the study.

Nursing methods

Patients in the CG were intervened by routine detailed behavioral nursing. Following the doctor's advice, patients were instructed to stay in bed or carry out appropriate activities. Besides, their body temperature and pulse were monitored on time until discharge, and their conditions were closely observed.

Patients in the SG received health concept model-based detailed behavioral care. Before carrying out the nursing work, the nursing staff introduced the disease to the elderly patients in detail, and guided them to relax and cooperate with the care. In addition, each patient's condition and physical function were assessed in a timely manner by means of echocardiography and 24-h continuous ECG monitoring, and the corresponding nursing plan was formulated based on the evaluation results. Furthermore, medication management was strengthened. The patient's indicators (*e.g.*, blood pressure and blood lipid) were strictly monitored and controlled within the reference range as far as possible to prevent complications. The emotional status of patients was always concerned during daily care. When they were found to develop NEs, the causes of unhealthy psychological states were analyzed in time, based on which targeted psychological nursing intervention was developed and implemented. During the nursing intervention, patients' bad daily behavioral habits were corrected, and they were guided to keep good hours to reduce the burden on their hearts. In addition, a certain amount of exercise was also ensured, which was realized by developing an appropriate exercise program for each patient to help improve his/her physical fitness and blood circulation. Moreover, a reasonable diet plan was formulated based on the patient's nutritional status and physical function. In the daily diet, patients were advised to take easy-to-digest, crude fiber, and light foods, and avoid oily and high-fat foods.

Outcome measures

The rehabilitation of the two groups of patients after nursing was compared. It was considered markedly effective if the patient had CF improvement ≥ grade II, with obviously improved condition. Effective referred to CF improvement > grade I and alleviation of clinical symptoms. Ineffective corresponded to CF improvement < grade I, non-improvement, or disease worsening[17]. Overall response rate was calculated as (markedly effective cases + effective cases)/total cases × 100%.

Alterations in CF indexes [left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), and left ventricular end systolic diameter (LVESD)] were compared before and after care.

Assessment of patients' anxiety and depression was performed 7 d after nursing using the self-rating anxiety/depression scale (SAS/SDS)[18]. Both scales have a total score of 100, with the scores in direct proportion to anxious and depressive symptoms.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ)[19], which comprises 3 dimensions and 21 items (8, 5, and 8 items in physical field, emotional field, and other fields, respectively), was used for QoL assessment of elderly CHF patients. The total score is 105 points, and the score is inversely proportional to the patient's QoL. Patients' overall nutritional status was evaluated by the Modified Quantitative Subjective Global Assessment (MQSGA) of nutrition[20], with a total score of 35 points, and the score is inversely proportional to the nutritional status.

Nursing satisfaction was investigated using the self-made nursing satisfaction questionnaire (total score: 100) from the aspects of comfort, health knowledge, working ability, service attitude, and comprehensive level. Patients or their families filled it out according to the actual situation. A score of > 90, 70-90, and < 70 points was considered as very satisfied, satisfied, and dissatisfied, respectively, and the total satisfaction = very satisfied + satisfied. The overall nursing satisfaction was compared.

Statistical analysis

In this study, SPSS 19.0 medical statistical analysis software was used to statistically analyze the collected data, with $P < 0.05$ regarded as the significance level for all analyses. The chi-square test (χ^2) was performed for counting data expressed as percentages (%). The mean ± SD was used to denote quantitative data, which all followed a normal distribution and were analyzed between groups by the independent sample *t* test and between different time points by the paired *t* test.

RESULTS

Patients' baseline data

Comparing patients' baseline data, it was found that the two patient cohorts were comparable in age, sex, course of disease, body mass index, systolic blood pressure, complications (hypertension, diabetes, coronary heart disease, and atrial fibrillation), CF grade[17], and heart rate ($P > 0.05$), as shown in Table 1.

Comparison of rehabilitation efficacy

Comparing the rehabilitation effects after intervention, it was found that the total rehabilitation effective rate in the SG

Table 1 Baseline data

		Study group (*n* = 62)	Control group (*n* = 54)	χ^2/t	*P* value
Age (years old)		78.16 ± 6.58	77.19 ± 6.94	0.772	0.442
Sex				1.400	0.237
	Male	40 (64.52)	29 (53.70)		
	Female	22 (35.48)	25 (46.30)		
Course of disease (years)		5.55 ± 1.34	5.43 ± 1.56	0.446	0.657
BMI (kg/m^2)		23.71 ± 3.27	23.93 ± 3.11	0.370	0.712
Systolic pressure (mmHg)		147.97 ± 12.45	149.94 ± 14.28	0.794	0.429
Complications					
	Hypertension	12 (19.35)	14 (25.93)	0.717	0.397
	Diabetes mellitus	8 (12.90)	10 (18.52)	0.694	0.404
	Coronary heart disease	29 (46.77)	23 (42.59)	0.204	0.652
	Atrial fibrillation	13 (20.97)	7 (12.96)	1.296	0.255
Cardiac function grade				2.772	0.250
	II	30 (48.39)	21 (38.89)		
	III	20 (32.26)	25 (46.30)		
	IV	12 (19.35)	8 (14.81)		
Heart rate (beats/min)		80.11 ± 5.24	80.98 ± 5.7	0.856	0.394

BMI: Body mass index.

Table 2 Rehabilitation efficacy

	Study group (*n* = 62)	Control group (*n* = 54)	χ^2	*P* value
Markedly effective	38 (61.29)	25 (46.30)		
Effective	21 (33.87)	20 (37.03)		
Ineffective	3 (4.84)	9 (16.67)		
Overall response	59 (95.16)	45 (83.33)	4.354	0.037

was 95.16%, significantly higher than that of the CG (83.33%; $P < 0.05$), as shown in Table 2.

CF improvement

The observation of patients' CF revealed no evident difference in LVEF, LVEDD, and LVESD between the two groups prior to nursing intervention ($P > 0.05$), while elevated LVEF and decreased LVEDD and LVESD were found in both cohorts post intervention ($P < 0.05$). And in comparison with the CG, LVEF was higher while LVEDD and LVESD were lower in the SG ($P < 0.05$; Figure 1).

Relief of patients' NEs

We comparatively analyzed the relief of patients' NEs and found significantly reduced SAS and SDS scores in both cohorts after intervention ($P < 0.05$), with more significant reductions in the SG compared with the CG ($P < 0.05$; Figure 2).

Improvement of nutritional status and QoL of patients after nursing

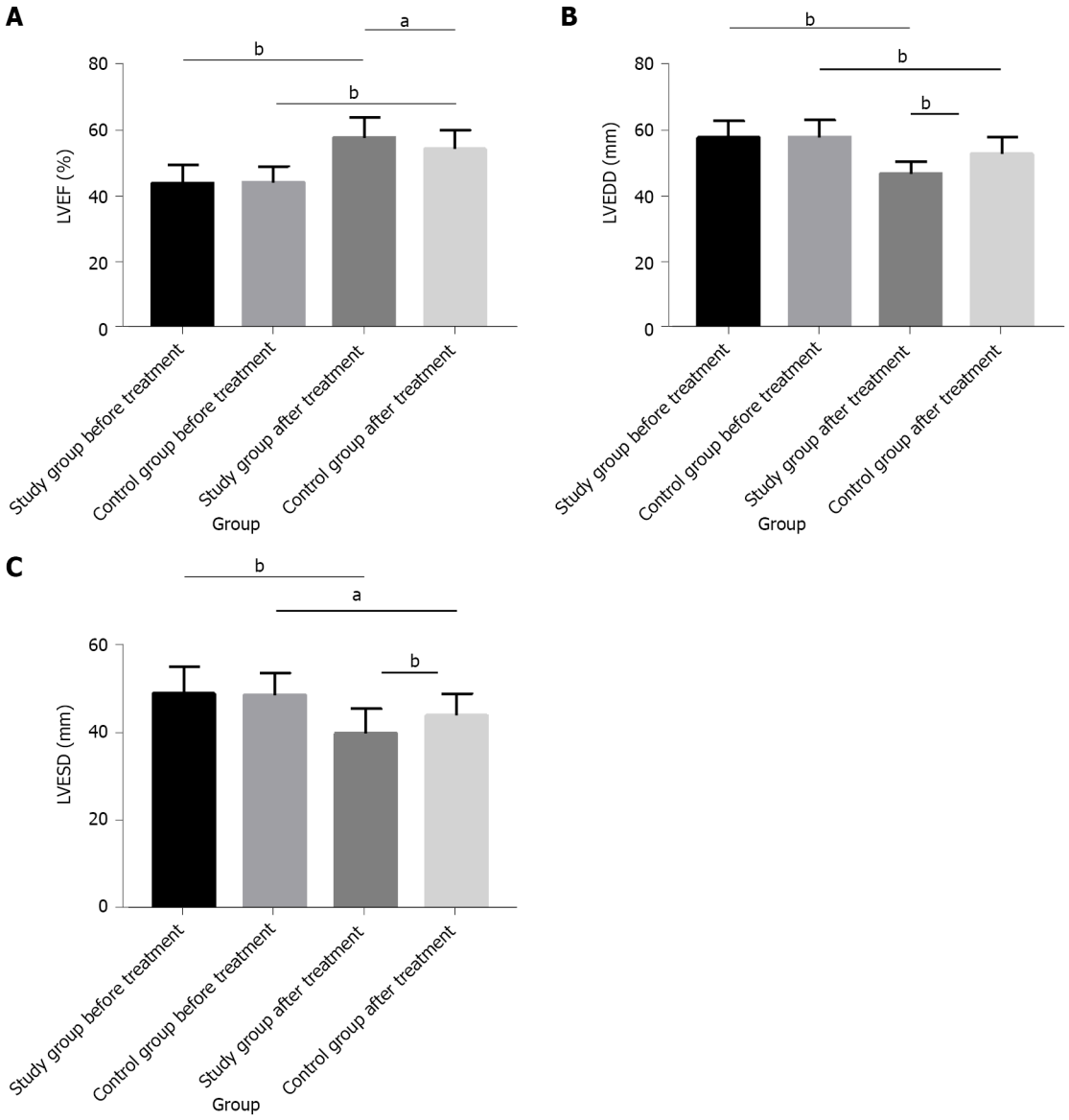
Comparing the MQSGA and MLHFQ scores before and after patient care, it was found that both scores decreased after nursing ($P < 0.05$), with more significant reductions in the SG as compared to the CG ($P < 0.05$; Figure 3).

Comparison of patients' nursing satisfaction

Statistics on patient satisfaction revealed a nursing satisfaction of 93.55% in the SG, statistically higher than that of the CG (81.48%; $P < 0.05$; Table 3).

Table 3 Nursing satisfaction

	Study group (*n* = 62)	Control group (*n* = 54)	χ^2	*P* value
Very satisfied	35 (56.45)	27 (50.00)		
Satisfied	23 (37.10)	17 (31.48)		
Dissatisfied	4 (6.45)	10 (18.52)		
Total satisfaction	58 (93.55)	44 (81.48)	3.960	0.047

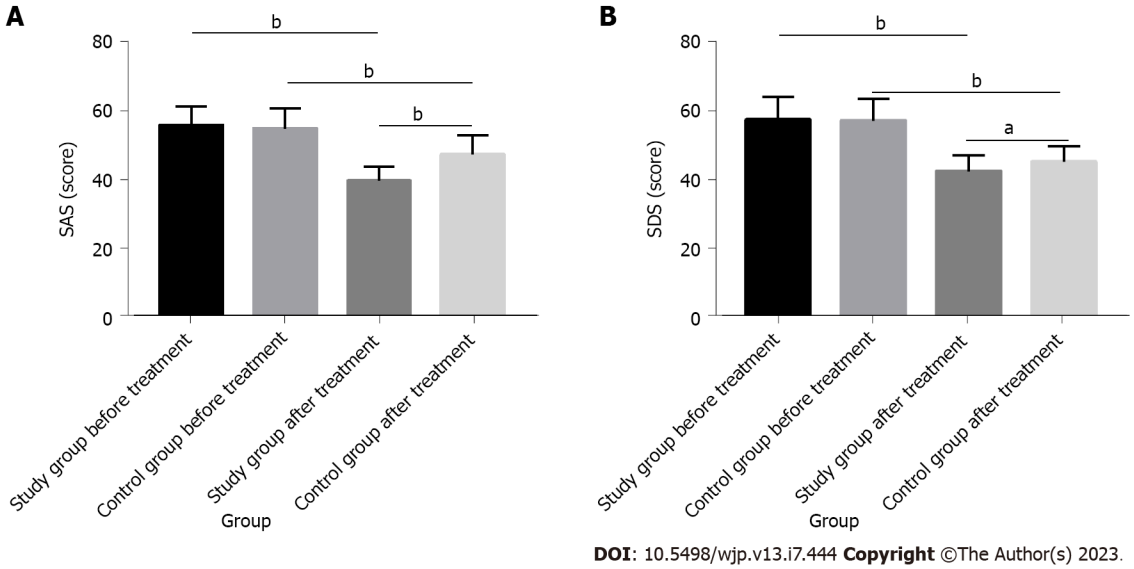


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Figure 1 Comparison of patients' cardiac function. A: After nursing, the left ventricular ejection fraction of patients in both groups were significantly improved, with a higher level in the study group as compared to the control group; B: Left ventricular end diastolic diameter was significantly reduced in both groups after nursing, and was statistically lower in the study group compared with the control group; C: After nursing, left ventricular end systolic diameter in the two groups dropped obviously and was lower in the study group compared with the control group. [a]*P* < 0.01; [b]*P* < 0.001. LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter.

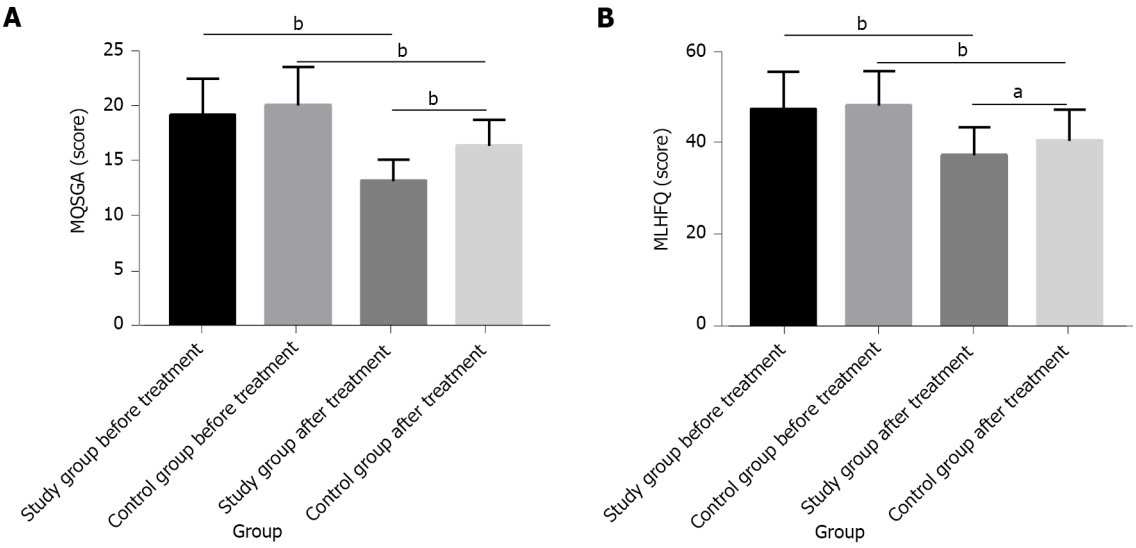
DISCUSSION

Due to CF abnormalities, CHF patients experience many physiological and psychological problems such as restricted daily activities, disordered sleep patterns, and depression, resulting in the need of care from family members in daily life [21]. However, there may be unsatisfactory nursing effects due to inadequate nursing training of family caregivers, and improper care may adversely impact patients both physically and psychologically. Educational interventions can



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Figure 2 Comparison of patients' negative emotions. A: After nursing, the self-rating anxiety scale score of both groups of patients dropped markedly and was lower in the study group compared with the control group; B: The self-rating depression scale score decreased statistically in both groups after nursing and was lower in the study group compared with the control group. [a]*P* < 0.01; [b]*P* < 0.001. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.



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Figure 3 Improvement of nutritional status and quality of life of patients. A: The modified quantitative subjective global assessment score of the two groups dropped statistically after nursing, and was lower in the study group compared with the control group; B: After nursing, the Minnesota living with heart failure questionnaire score of the two groups dropped statistically and was lower in the study group compared with the control group. [a]*P* < 0.01; [b]*P* < 0.001. MQSGA: Modified quantitative subjective global assessment; MLHFQ: Minnesota living with heart failure questionnaire.

effectively improve people's awareness of various health issues, thus affecting patients' detailed behaviors. In recent years, an increasing number of researchers have devoted themselves to exploring a better nursing intervention model for CHF. For example, Taniguchi *et al*[22] adopted a self-monitoring outpatient care model for CHF patients, and Jin *et al*[23] suggested cluster care in their study[22,23].

This study put forward the view that health concept model-based detailed behavioral care can better promote the rehabilitation of elderly CHF patients and improve their CF than the routine one. Previous studies have also shown that interventions based on the health concept model can accelerate recovery from chronic diseases[24]. In addition, under the health concept model-based detailed behavioral care, appropriate exercise programs will be developed for patients, with the exercise intensity gradually increased according to the patient's tolerance, thus facilitating patient recovery. It has been shown that CF recovery in heart failure patients is accelerated with increasing intensity of exercise training. However, too much exercise in a short period of time will lead to poor exercise experience, reduced comfort, and increased NEs, which cannot motivate patients' treatment and compliance[25,26]. Therefore, we increased the amount of exercise step by step to play a better role in rehabilitation.

Middle-aged and aged people are more susceptible to coronary heart disease as their physical fitness will be partially degraded with age, which will affect their physical resistance and psychological status, reducing their QoL[27]. The detailed behavior nursing based on the health concept model can mitigate patients' NEs while enhancing their nutritional status and QoL. The introduction of a more nutritious diet into daily life, coupled with effective rehabilitation, resulted in significant improvements in the patient's nutritional status, QoL, and NEs. Li *et al*[28] mentioned in their study that intervention based on the health concept model can effectively improve the self-management ability of patients and enhance their professional knowledge during the intervention process, contributing to enhanced confidence in treatment and better QoL, which is similar to our research. In addition, detailed nursing can reflect the quality of care services. Nursing disputes arising from nursing defects, errors, and accidents should be effectively avoided during clinical treatment and nursing care. Meanwhile, ward inspections should be strengthened during treatment, so as to ensure nursing safety, enhance nursing service quality, and improve patient satisfaction[29,30]. In our research, health concept model-based detailed behavioral care also significantly outperformed conventional detailed behavioral nursing in terms of patient satisfaction, consistent with the satisfaction results of Smeulders *et al*[31] on patients with heart failure.

The novelty of this study lies in the comparative analysis of the clinical differences in the rehabilitation effect, CF, SAS, SDS, nutritional status, QoL, and nursing satisfaction between health concept model-based detailed behavioral care and routine detailed behavioral nursing in elderly CHF patients. However, this study also has some limitations. CHF is a long-term condition, but patient outcomes have not been explored in this study, resulting in little understanding of the impact of this care model on patient prognosis. Second, we only included patients aged over 60 years, since the elderly were the main patient group of CHF. However, it is still unclear whether our intervention methods are also applicable to those younger than 60 years, which needs to be explored by re-incorporating samples in subsequent studies.

CONCLUSION

In conclusion, health concept model-based detailed behavioral care has high application value in elderly CHF patients, which can improve patients' rehabilitation efficiency, significantly mitigate NEs, and enhance their CF and QoL.

ARTICLE HIGHLIGHTS

Research background

Chronic heart failure (CHF), a clinical condition that affects a large proportion of the elderly population, is characterized by a long course of disease, many complications, and decreased self-care ability, often bringing a huge economic burden to the families of patients and society.

Research motivation

To help people understand CHF in the elderly and provide reference for the clinical optimization of this disease.

Research objectives

To evaluate the application value of health concept model-based detailed behavioral care in elderly patients with CHF.

Research methods

Sixty-two cases of CHF who underwent health concept model-based detailed behavioral care were included in a study group, and patients' rehabilitation efficiency, negative emotions (NEs), cardiac function (CF) parameters, nutritional status, quality of life (QoL), and nursing satisfaction were recorded. In addition, 54 cases who underwent routine detailed behavioral care were included in a control group (CG) for analysis.

Research results

The rehabilitation efficiency and CF parameters of the study group were significantly improved after intervention. In addition, more significant alleviation in NEs and improvement in QoL were recorded in the study group as compared to the CG. A higher degree of overall nursing satisfaction was also noted in the research group.

Research conclusions

Health concept model-based detailed behavioral care has high application value in elderly patients with CHF, which can improve patients' rehabilitation efficiency, significantly relieve NEs, and enhance their CF and QoL.

Research perspectives

This study discusses the application value of health concept model-based detailed behavioral care in the nursing of elderly CHF patients, and focuses on patients' NEs and QoL, hoping to provide some references for improving the clinical care of such patients.

FOOTNOTES

Author contributions: Zheng AD and Xu J carried out the studies, and conceived and designed the study; Zheng AD and Cai LL performed the analyses and collected the data; Zheng AD drafted the manuscript; all authors approved the final manuscript submitted.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Retrospective Study

Repetitive transcranial magnetic stimulation combined with olanzapine and amisulpride for treatment-refractory schizophrenia

Jin-Ling Liu, Zhi-Mei Tan, Shu-Jie Jiao

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Abstract

BACKGROUND

Treatment-refractory schizophrenia (TRS), accounting for approximately 30% of all schizophrenia cases, has poor treatment response and prognosis despite treatment with antipsychotic drugs.

AIM

To analyze the therapeutic effectiveness of repetitive transcranial magnetic stimulation (rTMS) combined with olanzapine (OLZ) and amisulpride (AMI) for TRS and its influence on the patient's cognitive function.

METHODS

This study enrolled 114 TRS patients who received treatment at the First Affiliated Hospital of Zhengzhou University between July 2019 and July 2022. In addition to the basic OLZ + AMI therapy, 54 cases of the control group (Con group) received modified electroconvulsive therapy, while 60 cases of the research group (Res group) received rTMS. Data on therapeutic effectiveness, safety (incidence of drowsiness, headache, nausea, vomiting, or memory impairment), Positive and Negative Symptom Scale, Montreal Cognitive Assessment Scale, and Schizophrenia Quality of Life Scale were collected from both cohorts for comparative analyses.

RESULTS

The Res group elicited a higher overall response rate and better safety profile when compared with the Con group. Additionally, a significant reduction was observed in the post-treatment Positive and Negative Symptom Scale and Schizophrenia Quality of Life Scale scores of the Res group, presenting lower scores than those of the Con group. Furthermore, a significant increase in the Montreal

Cognitive Assessment Scale score was reported in the Res group, with higher scores than those of the Con group.

CONCLUSION
The treatment of TRS with rTMS and OLZ + AMI is effective and safe. Moreover, it can alleviate the patients' mental symptoms, improve their cognitive function and quality of life, and has a high clinical application value.

Key Words: Repetitive transcranial magnetic stimulation; Olanzapine; Amisulpride; Treatment-refractory schizophrenia; Therapeutic effectiveness; Cognitive function

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Core Tip: Patients with treatment-refractory schizophrenia always have an unsatisfactory treatment response and prognosis despite antipsychotic therapy, which poses significant challenges to clinical management. Therefore, it is necessary to continuously explore and validate effective treatments for treatment-refractory schizophrenia.

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INTRODUCTION

Schizophrenia, a heterogeneous progressive mental illness that may lead to cognitive impairment in patients, has a great negative impact on the patient's social interaction and work[1]. The etiology of the disease is complicated and has been linked to environmental factors, hereditary factors, cortical excitation-to-inhibition imbalance, and subcortical dopamine dysfunction[2]. Schizophrenia is prone to occur in early adulthood, and its symptoms are classified as positive symptoms, such as hallucinations, delusions, and speech disorders, and negative symptoms, such as emotional retardation, abulia, and social barriers[3]. The overall prevalence of schizophrenia is approximately 0.4%, and the mortality rate of schizophrenia patients is 2-4 times that of the general population[4,5]. Treatment-refractory schizophrenia (TRS), accounting for approximately 30% of the total schizophrenia cases, has a poor treatment response and prognosis despite treatment with antipsychotic drugs, which also poses great clinical challenges[6,7]. Nevertheless, it is a compelling responsibility of physicians to explore effective treatment options for TRS.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation method, induces local neuronal activation in the brain regions *via* electromagnetic induction of electric fields, thus ameliorating the abnormal connections between the brain regions to a certain extent[8,9]. According to the research by Zhu *et al*[10], rTMS has a significant long-term ameliorating effect on working memory defects in schizophrenia patients. Olanzapine (OLZ) and amisulpride (AMI) are both first-line antipsychotic drugs, which are highly effective in reducing the Positive and Negative Syndrome Scale (PANSS) scores and alleviating the mental symptoms of the patients[11]. OLZ is a 5-hydroxytryptamine 2A/2C antagonist affecting the glucolipid metabolism[12] and an efficient AMP-activated protein kinase activator that enhances the AMP-activated protein kinase activity in the hypothalamus, thus mediating energy homeostasis and metabolic modulation during neuronal activity[13,14]. As for AMI, it is beneficial in relieving depressive symptoms and major negative symptoms as well as enhancing the patient's quality of life (QOL)[15].

We proposed that the combination of rTMS and OLZ + AMI has certain beneficial clinical effects in TRS patients.

MATERIALS AND METHODS

Patient information

This study selected 114 TRS patients who received treatment at the First Affiliated Hospital of Zhengzhou University between July 2019 and July 2022. Among them, 54 cases were included in the control group (Con group) treated with modified electroconvulsive therapy (mECT) and 60 cases in the research group (Res group) treated with rTMS; the patients in both groups received OLZ + AMI therapy. The patients in the Res and Con groups presented similar demographic data ($P > 0.05$), suggesting clinical comparability and feasibility during follow-up research.

Inclusion criteria: The inclusion criteria for this study were that patients of both groups fulfill the TRS diagnostic criteria and present complete medical records with no treatment-associated contraindications.

Exclusion criteria: Patients with a history of allergy to the study medications, serious diseases such as heart, lung, or kidney dysfunction, and mental retardation that hindered compliance and cooperation were excluded. Furthermore, pregnant and lactating women and drug abusers were excluded from this study.

Methods

The Con group patients were treated with mECT and OLZ + AMI, as described here. The patients received mECT 2-3 times a week using a Thymatron ECT therapeutic apparatus. The treatment frequency could be adjusted to once weekly according to the treatment effect up to a maximum of 8 times during the treatment course. The initial oral dose of OLZ was 5 mg once daily, and the drug dose could be gradually increased to 10-15 mg/d, depending on patient tolerance, for a total period of 8 wk. AMI was administered orally at an initial dose of 200 mg/d and increased according to patient tolerance and efficacy but not beyond a maximum daily dose of 1200 mg for a total period of 8 wk.

The Res group received rTMS combined with OLZ + AMI. An rTMS therapeutic instrument was used for treatment. The coil of the instrument was placed on the patient's forehead on the left, tangential to the scalp. The dorsolateral left frontal lobe was stimulated according to the threshold stimulation intensity of 80%-110% of the motor threshold, and the frequency was set at 20 Hz. The treatment time was 20 min, once a day, 5 times a week for 8 wk. OLZ and AMI were administered in the same way as that in the Con group.

Outcome measures

Clinical effectiveness: The PANSS scores were compared before and after treatment between the Res and Con groups. A decrease of more than 80% in the PANSS score was considered a "marked response," a decrease of 50%-79% was considered a "response," and failure to meet the above reduction criteria was considered as "non-response." The overall response rate (ORR) was the percentage of the sum of the number of "marked response" and "response" patients among the total number of cases.

Safety: We observed and recorded the number of cases of drowsiness, headache, nausea, vomiting, and memory impairment and calculated the overall incidence.

Severity of schizophrenia: All patients were assessed for schizophrenia severity using the PANSS (total score: 98) with positive and negative subscales. The higher the score, the more serious the symptoms of schizophrenia.

Cognitive function: The cognitive function (CF) of patients was evaluated using the Montreal Cognitive Assessment (MoCA), comprising eight items such as visuospatial/executive ability, memory, naming, and attention. On the 30-point scale, lower scores suggested worse CF.

QOL: The QOL of schizophrenia patients was evaluated using the Schizophrenia Quality of Life Scale (SQLS), comprising psychosocial factors (15 items, total score: 60), motivation and energy (7 items, total score: 28), and symptoms and adverse reactions (8 items, total score: 32). The score was inversely associated with the patient's QOL.

Statistical analysis

This study used Statistical Product and Service Solutions version 19.0 for data analysis; P-values < 0.05 were considered statistically significant. Sex and other categorical variables, expressed as the number of cases/percentages (n/%), were compared between the groups using the χ^2 test. Continuous variables, such as the PANSS scores, expressed as means ± standard error, were compared between the groups using the t-test.

RESULTS

General information

Sex, age, course of the disease, family history, marital status, and educational level did not differ significantly between the Res and Con groups, indicating possible comparability between them (P > 0.05) (Table 1).

Comparison of therapeutic effectiveness

The ORRs of the Con and Res groups were 72.22% and 93.33%, respectively, demonstrating significantly higher efficacy of rTMS and OLZ + AMI than that of mECT and OLZ + AMI (P < 0.05) (Table 2).

Comparison of safety

Observation and records of the occurrence of drowsiness, headache, nausea, vomiting, and memory impairment in both cohorts showed that the incidence of adverse events was statistically higher in the Con group than in the Res group (25.93% *vs* 8.33%, P < 0.05) (Table 3).

Comparison of mental symptoms

Analysis of the mental symptoms using the PANSS revealed that the scores did not differ significantly between the groups before treatment (P > 0.05). However, the scores reduced significantly after treatment in both groups (P < 0.05), with the Res group exhibiting lower scores than those of the Con group (P < 0.05) (Figure 1A).

Comparison of CF

CF, analyzed using the MoCA, did not differ significantly between the groups before treatment (P > 0.05). However, the MoCA scores increased significantly in both cohorts after treatment (P < 0.05), with higher scores in the Res group than in the Con group (P < 0.05) (Figure 1B).

Table 1 Demographic information

Categories	Control group, *n* = 54	Research group, *n* = 60	χ^2/t value	*P* value
Sex			0.069	0.793
Male	32 (59.26)	37 (61.67)		
Female	22 (40.74)	23 (38.33)		
Age in yr	40.07 ± 7.01	41.28 ± 8.74	0.810	0.420
Course of the disease in yr	19.56 ± 7.55	18.93 ± 5.83	0.501	0.617
Family medical history			0.252	0.616
Yes	6 (11.11)	5 (8.33)		
No	48 (88.89)	55 (91.67)		
Marital status			0.381	0.537
Married	33 (61.11)	40 (66.67)		
Single	21 (38.89)	20 (33.33)		
Educational level			1.481	0.224
Below high school	30 (55.56)	40 (66.67)		
High school and above	24 (44.44)	20 (33.33)		

Data are presented as *n* (%), unless otherwise indicated.

Table 2 Comparison of the therapeutic effectiveness of the two treatment methods

Indicators	Control group, *n* = 54	Research group, *n* = 60	χ^2 value	*P* value
Marked response	19 (35.19)	36 (60.00)	-	-
Response	20 (37.04)	20 (33.33)	-	-
Non-response	15 (27.78)	4 (6.67)	-	-
Overall response	39 (72.22)	56 (93.33)	9.120	0.003

Data are presented as *n* (%).

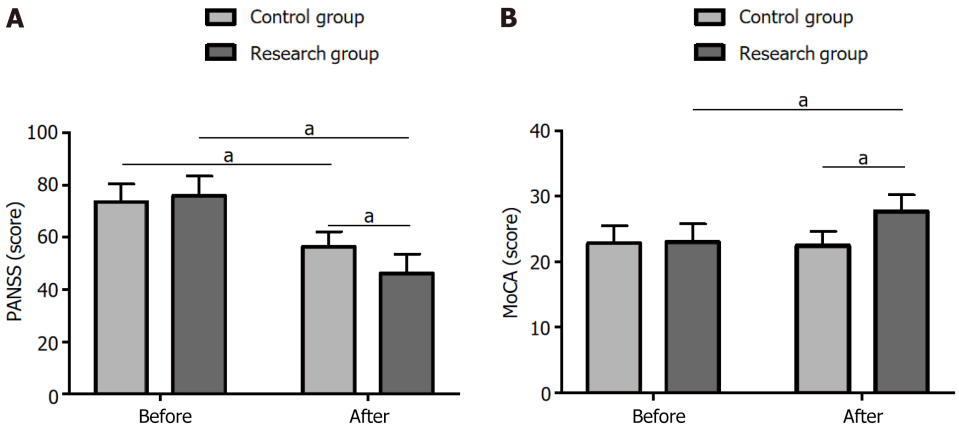
Table 3 Comparison of the safety of the two treatment methods

Indicators	Control group, *n* = 54	Research group, *n* = 60	χ^2 value	*P* value
Drowsiness	4 (7.41)	1 (1.67)	-	-
Headache	4 (7.41)	1 (1.67)	-	-
Nausea	3 (5.56)	2 (3.33)	-	-
Vomiting	2 (3.70)	1 (1.67)	-	-
Memory impairment	1 (1.85)	0 (0.00)	-	-
Total	14 (25.93)	5 (8.33)	6.333	0.012

Data are presented as *n* (%).

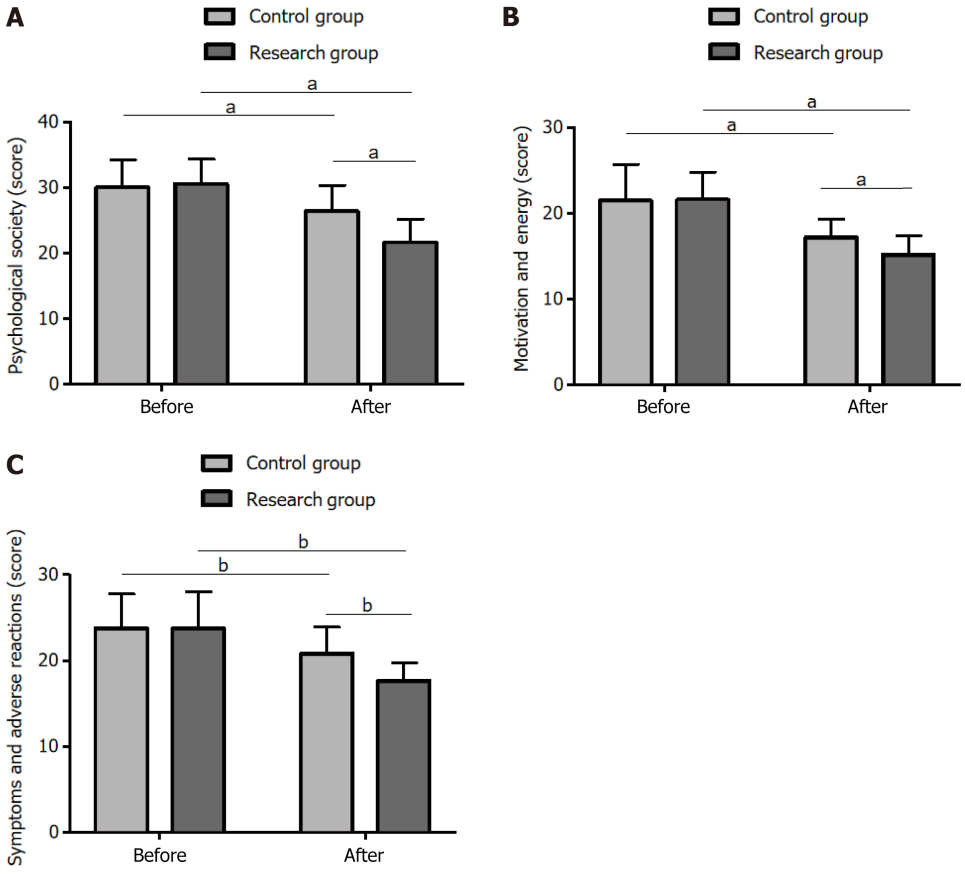
Comparison of QOL

The QOL assessment using the SQLS showed that the two groups did not differ statistically in the QOL before treatment ($P > 0.05$). However, the post-treatment QOL improved significantly, manifesting as significantly reduced SQLS scores in various dimensions ($P < 0.05$), with the Res group exhibiting better QOL (lower SQLS scores) than that of the Con group ($P < 0.05$) (Figure 2).



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Figure 1 Comparison of the mental symptoms and the cognitive function between the groups. A: Comparison of the mental symptoms; B: Comparison of the cognitive function. MoCA: Montreal Cognitive Assessment; PANSS: Positive and Negative Syndrome Scale. $^{a}P < 0.05$.



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Figure 2 Comparison of the quality of life between the groups. A: Comparison of the quality of life between the two groups from the psychosocial society aspect; B: Comparison of the quality of life between the two groups from the motivation and energy aspect; C: Comparison of the quality of life between the two groups from the aspect of symptoms and adverse reactions. $^{a}P < 0.05$; $^{b}P < 0.01$.

DISCUSSION

TRS, a chronic mental disorder, is associated with an increased risk of metabolic syndrome, including hypertension and diabetes, as well as cardiovascular diseases and death in patients[16]. The difficulty in treating this disease lies in the fact that a significant proportion of patients do not respond well to non-clozapine antipsychotic drugs, ECT, or other enhancement strategies, imposing an economic burden on families and the healthcare system[17,18].

This study comparatively analyzed the effectiveness and safety of two treatment modalities for TRS, mECT and OLZ + AMI (Con group) *vs* rTMS and OLZ + AMI (Res group), to provide clinical support and references for the formulation of effective treatment strategies for TRS patients to improve their clinical outcomes and reduce medical costs. Our research results identified a significantly higher ORR in the Res group than in the Con group (93.33% *vs* 72.22%), indicating the superior therapeutic effectiveness of rTMS and OLZ + AMI than that of mECT and OLZ + AMI for TRS. Kahn *et al*[19] reported that 45% of the 93 patients receiving AMI and 44% of those receiving OLZ achieved "response" in the first stage of treatment, indicating that AMI or OLZ monotherapy induced less than satisfactory effects in TRS patients.

Currently, there are limited studies on AMI + OLZ combination therapy, most of which focus on the comparison of AMI or OLZ monotherapy. For instance, Men *et al*[20] demonstrated equivalent clinical efficacy and safety of AMI and OLZ in the treatment of schizophrenia. In our study, the total incidence of drowsiness, headache, nausea, vomiting, and memory impairment was significantly lower in the Res group than in the Con group (8.33% *vs* 25.93%), suggesting that rTMS contributes to fewer adverse events and is more cost-effective when compared with mECT in the treatment of TRS patients.

Additionally, we analyzed and compared the mental symptoms, CF, and QOL of the cohorts before and after treatment using the PANSS, MoCA, and SQLS, respectively. The Res group showed significantly reduced PANSS and SQLS scores after treatment. Moreover, the post-treatment scores in the Res group were significantly lower than those before treatment and those in the Con group. On the other hand, the MoCA scores increased significantly in the Res group, and the post-treatment scores were higher than those before treatment and those in the Con group. This suggests that the combination of rTMS and OLZ + AMI has a significant effect on the improvement of mental symptoms, CF, and QOL in TRS patients.

An open-label clinical study indicated that OLZ and AMI have positive and equivalent effects on ameliorating the negative symptoms and cognitive impairment in schizophrenia patients[21]. Currently, antipsychotics alone cannot fully relieve social cognitive impairment and enhance functional outcomes in patients with mental illnesses, while rTMS is highly effective in improving their CF and mental symptoms[22]. Li *et al*[23] reported that a combination of rTMS and family intervention plays a synergistic role in schizophrenia patients, which is conducive to ameliorate the patients' negative symptoms and CF.

Additionally, an animal study confirmed that rTMS elicits an antidepressant effect by enhancing the endogenous cannabinoid signaling transduction and upregulating the endogenous cannabinoid 1 receptor and diacylglycerol lipase-α in the hippocampal astrocytes and neurons in rats under chronic and unpredictable stress[24]. It has also been noted that rTMS may modulate the cortical plasticity by affecting the permanent changes in the excitability of the cerebellar-thalamic-cortical pathway and that its mechanism of action in TRS could be related to its promotion of interconnection of the remote areas in the neural network system[25].

This study had several limitations that require further consideration. First, this was a single-center retrospective study; hence, the inclusion of more cases from multiple centers would be beneficial to improve the accuracy of the research results. Second, basic experiments should be supplemented to explore the underlying mechanism of the combination of rTMS and OLZ + AMI in treating TRS to understand this therapy and TRS better. Finally, the supplement of multivariate analyses influencing the efficacy of rTMS and OLZ + AMI in the treatment of TRS will help gain deeper insights regarding the pathways to enhance treatment efficacy. Future studies improving the aforementioned limitations are warranted.

CONCLUSION

rTMS in combination with OLZ + AMI may be preferred over the combination of mECT and OLZ + AMI for treating TRS, as the former has a clinical ORR as high as 93.33% and an adverse event rate as low as 8.33%. Moreover, this therapy has outstanding effects in relieving mental symptoms and improving CF and QOL; hence, it should be considered widely in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Treatment-refractory schizophrenia (TRS) accounts for approximately 30% of all patients with schizophrenia, with unsatisfactory treatment response and poor patient prognosis despite antipsychotic therapy.

Research motivation

The treatment of TRS is difficult and challenging, but it is still the responsibility of doctors to explore effective treatment options for the disease.

Research objectives

To analyze the therapeutic effectiveness of repetitive transcranial magnetic stimulation (rTMS) combined with olanzapine (OLZ) and amisulpride (AMI) for TRS and its influence on the patients' cognitive function (CF).

Research methods

First, 114 TRS patients who received treatment between July 2019 and July 2022 were selected. On the basis of OLZ + AMI therapy, 54 cases in the control group (Con group) received modified electroconvulsive therapy, and 60 cases in the research group (Res group) were given rTMS. Information on the therapeutic effectiveness, safety (drowsiness, headache, nausea, vomiting, and memory impairment), Positive and Negative Symptom Scale, Montreal Cognitive Assessment Scale, and Schizophrenia Quality of Life Scale were collected from both patient cohorts for competitive analyses.

Research results

A higher overall response rate and a better safety profile of treatment were determined in the Res group compared with the Con group. In addition, marked reductions in the Positive and Negative Symptom Scale and Schizophrenia Quality of Life Scale scores were found in the Res group after treatment, which were lower compared with the Con group. A significant increase in the Montreal Cognitive Assessment Scale score was observed in the Res group, with higher scores than the Con group.

Research conclusions

rTMS plus OLZ + AMI was effective and safe in the treatment of TRS, which can alleviate the patients' mental symptoms and improve their CF and quality of life, with clinical promotion value.

Research perspectives

rTMS plus OLZ + AMI, with both clinical efficacy and safety, may be more suitable for TRS patients than modified electroconvulsive therapy plus OLZ + AMI. This therapy has significant advantages in relieving psychiatric symptoms and improving CF and quality of life, which is worth promoting clinically.

FOOTNOTES

Author contributions: Liu JL and Jiao SJ contributed to the study conception and design, drafting the manuscript, and data analysis and interpretation; Liu JL and Tan ZM contributed to the study conception and critical revision of the article for important intellectual content; Liu JL contributed to the study conception and design and critical revision of the article for important intellectual content.

Institutional review board statement: This study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare having no conflicts of interest.

Data sharing statement: The data for this study can be obtained from the corresponding author upon request.

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ORIGINAL ARTICLE

Observational Study

Effects of cumulative COVID-19 cases on mental health: Evidence from multi-country survey

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Abstract

BACKGROUND

Depression and anxiety were both ranked among the top 25 leading causes of global burden of diseases in 2019 prior to the coronavirus disease 2019 (COVID-19) pandemic. The pandemic affected, and in many cases threatened, the health and lives of millions of people across the globe and within the first year, global prevalence of anxiety and depression increased by 25% with the greatest influx in places highly affected by COVID-19.

AIM

To explore the psychological impact of the pandemic and resultant restrictions in different countries using an opportunistic sample and online questionnaire in different phases of the pandemic.

METHODS

A repeated, cross-sectional online international survey of adults, 16 years and above, was carried out in 10 countries (United Kingdom, India, Canada, Bangladesh, Ukraine, Hong Kong, Pakistan, Egypt, Bahrain, Saudi Arabia). The online questionnaire was based on published approaches to understand the psychological impact of COVID-19 and the resultant restrictions. Five standardised measures were included to explore levels of depression [patient health questionnaire (PHQ-9)], anxiety [generalized anxiety disorder (GAD) assessment], impact of trauma [the impact of events scale-revised (IES-R)], loneliness (a brief loneliness scale), and social support (The Multi-dimensional Scale of Perceived Social support).

RESULTS

There were two rounds of the online survey in 10 countries with 42866 participants in Round 1 and 92260 in Round 2. The largest number of participants recruited from the United Kingdom (112985 overall). The majority of participants reported receiving no support from mental health services throughout the pandemic. This study found that the daily cumulative COVID-19 cases had a statistically significant effect on PHQ-9, GAD-7, and IES-R scores. These scores significantly increased in the second round of surveys with the ordinary least squares regression results with regression discontinuity design specification (to control lockdown effects) confirming these results. The study findings imply that participants' mental health worsened with high cumulative COVID-19 cases.

CONCLUSION

Whist we are still living through the impact of COVID-19, this paper focuses on its impact on mental health, discusses the possible consequences and future implications. This study revealed that daily cumulative COVID-19 cases have a significant impact on depression, anxiety, and trauma. Increasing cumulative cases influenced and impacted education, employment, socialization and finances, to name but a few. Building a database of global evidence will allow for future planning of pandemics, particularly the impact on mental health of populations considering the cultural differences.

Key Words: COVID-19; Mental health; Global research; International; Pandemic; Impact

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Core Tip: This study explores the effect of cumulative coronavirus disease 2019 cases on mental health, more specifically on anxiety, depression, and trauma. Negative impact on mental health was found internationally, with individuals struggling to receive support from mental health services. Results also show that as the pandemic continued, mental health scores got worse.

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INTRODUCTION

Depression and anxiety conditions both ranked among the top 25 leading causes of global burden of diseases in 2019 prior to the coronavirus disease 2019 (COVID-19) pandemic[1]. On January 30, 2020, the World Health Organization (WHO) declared a public health emergency of international concern and governments were urged to prepare for the global spread of COVID-19 from East Asia[2]. The COVID-19 pandemic affected, and in many cases threatened the health and lives of millions of people across the globe[2].

In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by 25%, and overall, the pandemic was estimated to have caused 137.1 (95%UI: 92.5–190.6) additional disability adjusted life years per 100000 population for Major Depressive Disorder and 116.1 per 100000 population (95%UI: 79.3–163.80) for anxiety disorders according to a scientific brief released by the WHO[3]. A number of factors have been implicated including, but not limited to, the stress of social and self-isolation, loneliness, restrictions due to lockdowns[4,5], fear of infection and death of self and near ones, grief and bereavement, worries regarding jobs and finances, as well as impact on education, relationships and on carers[6].

Long COVID described the presence of persistent symptoms following infection from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus[7]. This can last weeks or months after initial infection[7,8]. Common symptoms of long COVID include breathlessness, fatigue, headaches, and weakness as well as reduced quality of life[7, 9]. The most common mental health problems experienced by individuals with long COVID were anxiety, depression, and post-traumatic stress disorder (PTSD)[9,10]. A scoping review of 239 patients found that 3-mo post-COVID, 37.2% experienced PTSD, 35.6% experienced anxiety, and 46.9% were experiencing depression[11,12]. These effects were maintained at 6-mo[11]. Overall, symptoms were more prevalent in women and hospitalized patients[9]. A number of population groups have been shown to have been more adversely affected, including young people and women[7], individuals with vulnerabilities and pre-existing mental health conditions[9,11]. Evidence on healthcare workers, who were frontline during the pandemic has been equivocal with different studies showing a range of impact in this group[11, 13]. The greatest increases in depression and anxiety were found in places highly affected by COVID-19 as indicated by decreased human mobility and daily COVID-19 infection rates[3].

Each country across the globe has responded to the pandemic guided by their population, resources, number of cases, socio demographics, political landscape, and culture[14]. Given the unique situation we faced, the authors sought to explore the psychological impact of the pandemic and resultant restrictions in different countries, using an opportunistic sample and online questionnaire that was established at the beginning of the pandemic.

MATERIALS AND METHODS

Study design

This international study aimed to investigate and report the psychological impact of cumulative COVID-19 cases in the participant sites. A repeated, cross-sectional online international survey of adults, 16 years and above, was carried out in 10 countries (United Kingdom, India, Canada, Bangladesh, Ukraine, Hong Kong, Pakistan, Egypt, Bahrain, Saudi Arabia). The online questionnaire was based on published approaches, to understand the psychological impact of COVID-19 and the resultant restrictions. Five standardised measures were included to explore levels of depression [patient health questionnaire-9 (PHQ-9)][15], anxiety [generalized anxiety disorder (GAD)-7; Generalised Anxiety Disorder Assessment] [16], impact of trauma [the impact of events scale-revised (IES-R)][17], loneliness (a brief loneliness scale)[18], and social support (The Multi-dimensional Scale of Perceived Social support)[19]. Further details of the methodology are documented in earlier publications by the group[9,13].

Materials

The survey was repeated to capture the dynamic impact of the pandemic. The questionnaire was changed for each round depending on the stage of pandemic, government policies, and circumstances in each country at the time. In order to make the questionnaire relevant to each country, it was available in different languages and various adaptations were made to ensure that local culture and responses to the pandemic were considered. For this reason, each country published the questionnaire at a slightly different time and some of the questions were variable. As an example, the "Keyworker" status did not exist in many countries and was only used where relevant. Another example, in the Ukraine questionnaire version, the question about exceeding the recommended limits of alcohol was excluded because of the absence of such recommended limits.

Study distribution

In the United Kingdom, the survey was conducted thrice with the corresponding two rounds of the survey in the other countries. The dates of the surveys in the participant countries are noted below. The surveys were publicised to the general population including students and healthcare professionals through social media. Most countries collaborated internally to capture a wide population. As an example, the leads in Ukraine collaborated with Ukrainian organizations including Mental health for Ukraine Project, National Psychological Association of Ukraine, Ukrainian Association of Cognitive-Behavioural Therapy, and Zhytomyr State University to help further with dissemination. Due to the unusual circumstances of the time, this was the best way to disseminate the survey.

Southern Health NHS Foundation Trust in the United Kingdom led and co-ordinated the online survey with support from the participant countries. The survey was advertised to staff, patients, and the public with a weblink to the survey platform.

Data analysis

Cumulative COVID-19 case data has been derived from Microsoft Azure Open dataset, which is a population open dataset[20]. Mental health scores are derived from the online survey and is sample data. In both data, time is day. Although cumulative COVID-19 cases data is available daily (for around last two years), mental health scores in the study were not available for each day during that time. The availability of mental health scores on a specific day depended on whether the survey was conducted on that day by a participant.

The study has used regression analyses, using cross section data of all countries that participated in the study. Separate regression analysis was conducted for survey round 1 and 2. In both regressions, we used dummies for all individual characteristics listed in Table 1 as control variables. Vulnerabilities including requiring shielding, experience of coronavirus, pre-existing mental health conditions, and mental health support, had extremely low response rates therefore, we have recoded missing values into no category, to increase sample sizes in regressions.

In both regressions, the main independent variable, daily cumulative COVID-19 cases, is converted into million unit (by dividing COVID-19 case by 1000000). The purpose is to scale up its coefficients.

The relationship between average mental health scores and average cumulative COVID-19 cases maybe be contaminated or biased by lockdown effects. To control for such effects, we added lockdown dummy, trend and their interaction following the specification in regression discontinuity design (RDD).

RESULTS

Demographics

There were two rounds of the online survey in eight country groups as shown in Table 1. Egypt, Saudi Arabia, and Bahrain were analysed as a single group (labelled Arabic speaking countries). Hong Kong did not participate in the second round due to difficulties in recruitment. While there were three rounds in the United Kingdom, we have only used data from the corresponding two rounds with other participant countries. The United Kingdom has the largest number of participants in both rounds (29134 and 83851, respectively).

In the first round of the survey, participants who reported being healthcare professionals are higher in the United Kingdom (43%). In the second round, Arabic speaking countries had the highest number of participants who reported as healthcare professionals (66%), with a sample size of 909.

Age follows a bell shaped or downward distribution. Female participants were higher than male in most countries. In Canada, United Kingdom and Ukraine, most participants were White. Christian religion was reported the dominant religion in the Western countries. In round one in the Arabic speaking countries, most survey participants reported as Christians too. In most countries, survey participants did not report University education. Most survey participants lived in their own homes. Low proportion of participants reported experiencing COVID-19, but a high percent of participants followed social distancing guidelines. Most of the participants did not report any pre-existing physical health conditions. Alcohol consumption was reported by participants in Canada, United Kingdom, and Ukraine. Most participants did not report taking drugs. Majority participants did not report receiving support from mental health services. Where received, mental health support was reported through general practitioners and many participants did not respond to this question as it was only relevant if they reported experiencing mental health problems.

Mental health scales

Table 2 shows means and SD of PHQ-9, GAD-7 and IES-R by country and survey rounds, with number of respondents (*n*), missing observations and nonrespondents. In both rounds in each country, there were fewer respondents of PHQ-9 compared to nonrespondents. For the other two mental health scales, the gap between respondents and nonrespondents is not that large, with respondents being higher than nonrespondents in some cases. PHQ-9 can vary from 0 to 27, GAD-7 from 0 to 21, and IES-R from 0-88; however, average figures of PHQ-9 are lower than those of other two. IES-R has higher mean scores than others. Hong Kong, Indian, and Ukrainian participants have reported lower scores on the three scales compared with other countries. Bangladesh has highest mean scores on PHQ9, GAD7 and IES -R. All scores increased in round 2 of the surveys.

Cumulative COVID-19 cases

For each country, cumulative COVID-19 cases (the cumulative number of people who suffered coronavirus in official records) varied over time. Mental health scores (on the 3 scales: PHQ-9, GAD-7 and IES-R) in each country varied over time and by individuals' responses during the survey period.

Figure 1 shows a histogram of day/time by country. Two long bars in Bangladesh indicate that survey responses in both rounds were received during short windows, although the survey was open for three months each time in each site. The same pattern is seen in Canada and Hong Kong. Survey periods in Arabic speaking sites and Ukraine seem longer but scattered, meaning that for several days, survey data including mental health scores were not available during the three month period. India and Pakistan showed good density for moderately wider periods in round 1. United Kingdom showed the longest periods of survey responses in both rounds, which indicates that survey data including mental health

Table 1 Percent of categories in individual characteristics by country and survey rounds (1 and 2)

	Arabic		Bangladesh		Canada		China	India		Pakistan		United Kingdom		Ukraine	
	1	2	1	2	1	2	1	1	2	1	2	1	2	1	2
Observations	1121	909	299	746	8648	5920	178	1427	68	803	160	29134	83851	1256	606
	Percent of above observations														
Healthcare professional															
No	40	9	67	69	88	91	65	65	40	44	41	47	66	79	74
Yes	38	66	4	5	7	9	19	19	44	0	34	43	22	9	10
Missing	22	25	29	26	5	0	16	16	16	56	25	10	12	12	16
Age category															
Under 25	10	4	69	68	8	16	2	20	7	20	51	6	6	35	15
25-44	44	61	14	14	36	36	43	44	44	35	26	36	31	43	54
45-54	16	9	2	1	15	16	12	11	16	3	4	23	19	9	13
55 and over	7	3	1	1	37	32	26	13	21	2	1	26	34	2	3
Missing	22	22	14	17	5	0	17	13	12	40	18	10	11	11	15
White ethnicity															
No	77	21	92	89	20	21	9	88	88	81	73	9	15	3	3
Yes	1	57	0	0	76	78	79	0	0	0	0	82	74	88	82
Missing	22	22	8	11	4	0	12	12	12	19	27	10	11	9	15
Christian religion															
No	8	73	92	87	48	52	8	80	78	81	75	48	46	21	22
Yes	70	4	0	0	47	47	32	7	9	0	0	41	39	69	62
Missing	22	22	8	13	5	1	60	13	13	19	25	11	15	11	16
Gender															
Female	50	27	22	23	56	54	61	60	56	49	61	74	61	77	74
Male	28	51	68	63	39	45	24	27	31	31	18	15	26	13	9
Missing	22	22	10	14	5	1	15	13	13	20	21	11	13	11	16
Attended university															
No	78	79	91	88	51	53	85	38	79	80	83	90	89	90	85
Yes	0	0	0	0	43	47	0	50	9	0	0	0	0	0	0
Missing	22	21	9	12	6	0	15	13	12	20	18	10	11	10	15
Living at own home															
No	43	52	64	53	35	41	37	49	0	43	41	25	29	54	41
Yes	35	26	26	35	61	59	51	39	0	38	40	66	61	36	44
Missing	22	22	10	12	5	0	13	12	100	19	19	10	11	10	15
Vulnerable according to government category															
No	63	34	74	52	63	66	71	68	0	68	46	70	67	76	54
Age ≥ 70	1	40	9	36	15	34	5	7	0	2	31	4	21	1	29
Chronic disease	2	0	1	0	6	0	2	1	0	2	0	6	0	4	0
Diabetes	2	0	0	0	3	0	4	1	0	0	0	2	0	0	0
Other	3	0	3	0	7	0	1	2	0	3	0	5	0	3	0
Missing	28	26	13	12	6	0	16	19	100	25	23	13	12	16	17
Vulnerable according to government category and require shielding															

No	64	0	85	0	75	0	77	72	0	67	0	77	0	72	0
Yes	6	0	2	0	13	0	5	6	0	6	0	7	0	11	0
Missing	30	100	14	100	12	100	18	22	100	26	100	16	100	17	100
Whether experienced coronavirus															
No	23	0	42	0	28	0	58	35	0	28	0	22	0	31	0
Yes	49	29	40	23	63	12	26	43	25	43	48	64	25	52	47
Missing	28	71	17	77	8	88	16	22	75	29	53	14	75	17	53
Pre-existing mental health condition															
No	42	0	46	1	62	1	74	67	3	40	0	53	0	60	0
Yes	28	3	41	5	31	21	8	11	4	35	11	31	18	23	9
Missing	30	97	13	95	7	79	18	22	93	25	89	16	82	17	91
Drinking alcohol															
No	68	64	76	77	20	54	28	57	47	0	0	13	75	17	0
Yes	5	1	12	6	74	22	56	24	35	0	5	75	11	69	1
Missing	27	35	13	17	5	24	16	19	18	100	95	12	14	14	99
Whether taking drug															
No	71	65	81	73	83	86	79	78	82	71	69	85	83	83	77
Yes	0	4	8	11	12	14	6	2	1	3	6	2	3	3	2
Missing	28	31	11	15	5	0	15	20	16	26	25	13	13	14	21
Ever experienced suicidal thoughts															
No	9	61	70	69	67	77	74	68	66	55	55	59	60	60	53
Yes	62	7	18	16	27	23	10	12	16	19	18	27	26	24	28
Missing	29	32	13	15	6	1	16	21	18	26	27	13	14	16	19
Having mental health support from															
No support	18	1	27	3	13	4	6	5	3	30	4	14	5	13	2
Health service provider	6	1	5	1	11	6	2	3	1	8	3	12	8	6	5
Other	3	1	7	1	7	10	2	2	1	4	3	5	4	7	1
Missing	73	97	61	95	69	80	90	89	94	58	90	69	83	75	91

Each panel in a column shows percentages of categories/responses of a characteristic/question. Total respondents in each category were divided by observations shown at the beginning of the table and then multiplied by 100, to get the percentage.

scores were available for relatively more days in United Kingdom despite the fact that the survey was available for the same number of months at each site.

Daily cumulative COVID-19 cases (in million) have been plotted for each country, from April 1, 2020 to April 1, 2021 (Figure 2). As India had high COVID-19 cases, we have scaled down the COVID-19 cases by converting its unit into million, to raise the coefficients of cumulative COVID-19 case in regressions. United Kingdom also had high figures (reached nearly 10 million in March 2021). Ukraine and Canada reached relatively high figures. Other countries including Hong Kong had lower figures for cumulative COVID-19 cases. Therefore, the lines are relatively flat (near zero). Hong Kong had low figures at those periods as different countries had their spikes at different times. The figure shows downward movement of lines in India and United Kingdom, because COVID-19 cases were revised.

In survey data of the countries, scores of three mental health scales were available for several individuals in a day. They are reported as averages in a day. Country averages of those averages are taken to get single values in each day. Country average of cumulative COVID-19 cases are also taken. In Figure 3, scatter plots of average values of PHQ-9, GAD-7 and IES-R are shown in three different subplots. Average cumulative COVID-19 cases are plotted in line with three subplots. While left vertical axes measure the average cumulative COVID-19 cases, the right vertical axes measure three average values of mental health scores/indices. As mental health is an individual characteristic, average mental health scores fluctuated over time, and were not uniform like average cumulative COVID-19 cases. However, average mental health scores had less fluctuation/scatter at the beginning of each round (especially at the beginning of the second round). At that time, average mental health scores showed upward movement with average cumulative COVID-19 cases.

Table 2 Summary statistics of mental health scores by country and survey rounds

		PHQ-9		GAD-7		IES-R	
		Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Arabic	Mean	7.85	6.27	5.28	4.56	20.81	17.14
	SD	6.97	6.88	5.78	5.56	18.79	19.12
	n	596	481	596	486	539	430
	Missing	525	428	525	423	582	479
Bangladesh	Mean	8.07	7.45	5.76	5.45	23.28	21.86
	SD	5.79	6.91	5.38	5.69	18.08	20.35
	n	205	462	205	485	179	419
	Missing	94	284	94	261	120	327
Canada	Mean	6.11	6.97	4.40	4.94	15.10	16.96
	SD	6.44	6.70	5.32	5.46	17.87	18.24
	n	7653	5721	7684	5770	7329	5554
	Missing	995	199	964	150	1319	366
China	Mean	4.38		3.25		11.61	
	SD	4.91		4.20		13.63	
	n	127		124		117	
	Missing	51		54		61	
India	Mean	4.99	4.07	3.46	2.43	14.65	10.24
	SD	5.56	5.34	4.38	3.31	16.49	12.00
	n	820	41	823	42	741	38
	Missing	607	27	604	26	686	30
Pakistan	Mean	8.55	8.64	5.10	5.37	19.02	19.59
	SD	7.34	7.51	5.56	5.42	17.26	19.18
	n	412	85	413	90	376	75
	Missing	391	75	390	70	427	85
United Kingdom	Mean	7.70	8.21	5.46	6.04	17.01	19.19
	SD	6.47	7.03	5.51	5.92	17.51	18.93
	n	22166	64382	22343	65056	20780	59966
	Missing	6968	19469	6791	18795	8354	23885
Ukraine	Mean	6.63	7.81	4.17	5.02	14.93	15.55
	SD	6.10	6.51	4.65	5.20	15.34	15.41
	n	860	421	863	426	782	382
	Missing	396	185	393	180	474	224
Total	Mean	7.24	8.09	5.11	5.93	16.55	18.98
	SD	6.49	7.01	5.45	5.88	17.57	18.88
	n	32839	71593	33051	72355	30843	66864
	Missing	10027	20667	9815	19905	12023	25396

PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7.

In more scatter areas, such positive relation between average cumulative COVID-19 cases and average mental health scores is not seen. As less scatter zones showed a positive relation, we can expect an overall positive relation between them. To control for bias or contamination effect of lockdown, we added lockdown dummy, trend and their interaction



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Figure 1 Distribution of survey respondents over time, by country.

following the specification in RDD.

Table 3 shows lockdown and survey periods of participant countries in the study. In each round, we have made normalized trend by subtracting lockdown easing/withdraw dates of countries (as lockdown start dates do not fall in survey periods) from trend. Zero is a common cut-off date; based on that we made a discontinuity dummy (1 = above cut-off, 0 = below cut-off), that captured negative effects of lockdown or withdraw on mental health. To capture different slopes on either side of the cut-off, we took interaction of normalized trends and the discontinuity dummy.

Regression results

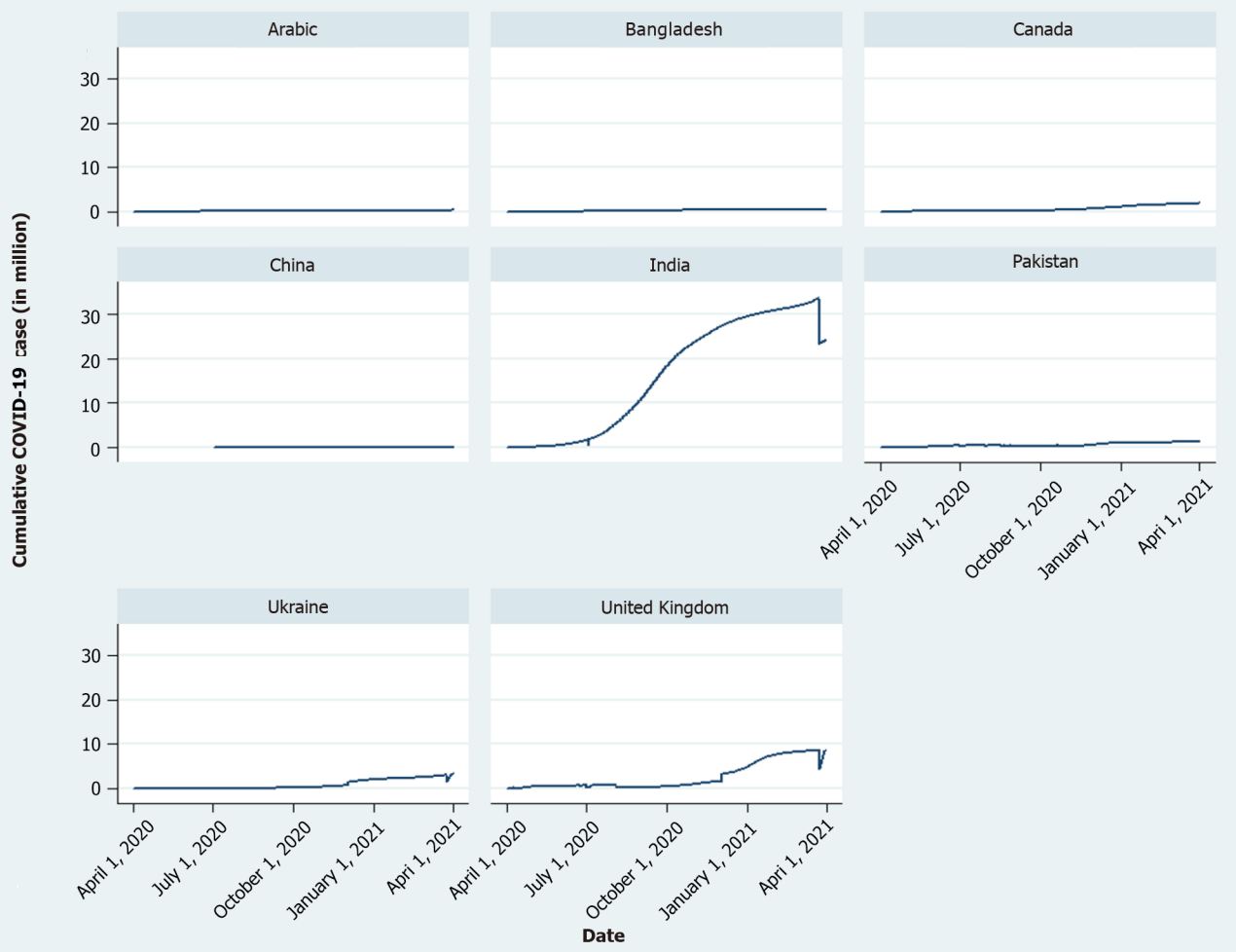
Table 4 shows regression results for round 1 and Table 5 for round 2. Both tables show two regression results for each mental health score/index, the dependent variable. The first one does not include RDD specification, while the second one does. When RDD specification is included, the results are for United Kingdom only.

In round 1, the cumulative COVID cases had statistically significant effect on all three mental health scores with RDD specification. For example, as United Kingdom had 7.70 average GAD-7, the increase size 1.75 in regression was nearly 23% (1.75 × 100/7.70). So, for a one million increase in cumulative daily COVID cases, GAD-7 increased by 23 percent.

In round 2 (Table 5), all three mental health indices increased statistically and significantly due to increase in cumulative COVID cases, with and without RDD specification. Without RDD specification, for a one million increase in cumulative COVID cases, the increase in PHQ-9 was 0.195 (2.38%), GAD-7 0.129 (2.14%), and IES-R 0.454 (2.37%). With RDD specification, for a one million increase in cumulative COVID cases, the increase in PHQ-9 was 0.433 (5.27%), GAD-7 0.577 (9.55%), and IES-R 1.265 (6.59%). Results with RDD specification implied that United Kingdom had higher effects than other countries.

Table 3 Lockdown and survey dates by country

Country	First lockdown		Second lockdown		Survey period		Can we capture lockdown effects?
	Start	End	Start	End	Round 1	Round 2	
Bangladesh	March 26, 2020	May 16, 2020	April 5, 2021	July 14, 2021	July 1, 2020-July 25, 2020	January 19, 2021-March 18, 2021	No
Canada	March 18, 2020	May 18, 2020	November 7, 2020	January 8, 2021	August 18, 2020-October 2, 2020	December 21, 2020-March 30, 2021	No
China	January 23, 2020	April 8, 2020			June 24, 2020-August 7, 2020		No
India	March 25, 2020	June 7, 2020	April 19, 2021	May 31, 2021	July 1, 2020-September 20, 2020	January 22, 2021-April 1, 2021	No
Pakistan	March 24, 2020	May 9, 2020	May 8, 2021	May 18, 2021	June 10, 2020-September 24, 2020	February 2, 2021-March 29, 2021	No
Saudi Arabia	March 29, 2020	June 21, 2020			June 3, 2020-October 7, 2020	January 16, 2021-April 1, 2021	Yes, in round 1
Ukraine	March 17, 2020	April 24, 2020			June 11, 2020-September 30, 2020	January 7, 2021-March 25, 2021	No
United Kingdom	March 23, 2020	July 4, 2020	November 5, 2020	December 2, 2020	April 28, 2020-August 6, 2020	November 12, 2020-February 18, 2021	Yes, in both rounds



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Figure 2 Cumulative coronavirus disease 2019 case (in million) over time, by country. COVID-19: Coronavirus disease 2019.

Table 4 Ordinary least squares regression of mental health scores on cumulative coronavirus disease 2019 case, lockdown, and individual characteristics (survey round 1)

	PHQ-9		GAD-7		IES-R	
	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Daily cumulative COVID-19 case/1000000	0.075[a]	2.121[c]	0.041	1.750[c]	0.225[a]	1.543[a]
	[-0.01, 0.16]	[1.58, 2.66]	[-0.03, 0.11]	[1.28, 2.22]	[-0.02, 0.47]	[-0.05, 3.14]
Dummy for first lockdown withdraw		-0.658[c]		-0.450[c]		-1.224[b]
		[-0.97, -0.34]		[-0.73, -0.17]		[-2.16, -0.29]
Dummy for first lockdown withdraw[1] (date-first lockdown withdraw date)		-0.018[c]		-0.014[c]		-0.043[c]
		[-0.03, -0.01]		[-0.02, -0.01]		[-0.07, -0.02]
Date-first lockdown withdraw date		0.006[b]		0.000		0.004
		[0.00, 0.01]		[-0.00, 0.01]		[-0.01, 0.02]
Healthcare professional (1 = yes, 0 = no)	-0.402[c]	-0.737[c]	-0.328[c]	-0.631[c]	-1.394[c]	-2.185[c]
	[-0.54, -0.26]	[-0.89, -0.58]	[-0.45, -0.21]	[-0.77, -0.49]	[-1.81, -0.98]	[-2.65, -1.72]
Age (base: Below 25)	0.000	0.000	0.000	0.000	0.000	0.000
25-44	-1.084[c]	-1.428[c]	-0.482[c]	-0.713[c]	-2.350[c]	-2.091[c]
	[-1.34, -0.83]	[-1.75, -1.11]	[-0.71, -0.26]	[-0.99, -0.43]	[-3.10, -1.60]	[-3.02, -1.16]
45-54	-1.958[c]	-2.345[c]	-1.456[c]	-1.737[c]	-3.992[c]	-3.366[c]
	[-2.24, -1.68]	[-2.69, -1.99]	[-1.70, -1.21]	[-2.05, -1.43]	[-4.83, -3.15]	[-4.39, -2.34]
55 and over	-2.956[c]	-3.108[c]	-2.179[c]	-2.284[c]	-5.568[c]	-4.085[c]
	[-3.24, -2.67]	[-3.47, -2.75]	[-2.43, -1.93]	[-2.60, -1.97]	[-6.42, -4.72]	[-5.15, -3.02]
White (1 = yes, 0 = no)	0.360[c]	0.482[c]	0.299[c]	0.413[c]	-1.120[c]	-0.054
	[0.17, 0.55]	[0.23, 0.74]	[0.13, 0.47]	[0.19, 0.64]	[-1.69, -0.55]	[-0.80, 0.69]
Christian (1 = yes, 0 = no)	-0.206[c]	-0.036	0.018	0.222[c]	0.522[c]	0.829[c]
	[-0.34, -0.07]	[-0.19, 0.12]	[-0.10, 0.13]	[0.08, 0.36]	[0.13, 0.91]	[0.37, 1.29]
Male (1 = yes, 0 = no)	-1.189[c]	-1.231[c]	-1.039[c]	-1.042[c]	-2.997[c]	-3.719[c]
	[-1.34, -1.03]	[-1.43, -1.03]	[-1.18, -0.90]	[-1.22, -0.86]	[-3.46, -2.53]	[-4.31, -3.13]
Attended university (1 = yes, 0 = no)	-1.141[c]	0.000	-0.545[c]	0.000	-1.254[c]	0.000
	[-1.34, -0.94]	[0.00, 0.00]	[-0.72, -0.37]	[0.00, 0.00]	[-1.85, -0.65]	[0.00, 0.00]
Living at own home (1 = yes, 0 = no)	-0.885[c]	-1.105[c]	-0.489[c]	-0.692[c]	-1.432[c]	-2.270[c]
	[-1.04, -0.73]	[-1.30, -0.91]	[-0.63, -0.35]	[-0.86, -0.52]	[-1.89, -0.97]	[-2.83, -1.71]
Vulnerable according to government category (base: Not vulnerable)	0.000	0.000	0.000	0.000	0.000	0.000
Aged 70 or above	-0.898[c]	-1.105[c]	-0.764[c]	-0.985[c]	-1.954[c]	-2.909[c]
	[-1.18, -0.62]	[-1.52, -0.69]	[-1.01, -0.52]	[-1.35, -0.62]	[-2.81, -1.10]	[-4.19, -1.63]
Chronic disease	0.361[b]	0.345[b]	0.533[c]	0.543[c]	1.245[c]	1.644[c]
	[0.08, 0.64]	[0.03, 0.66]	[0.29, 0.78]	[0.26, 0.83]	[0.41, 2.08]	[0.70, 2.59]
Diabetes	0.034	-0.064	0.102	0.139	0.867	1.185
	[-0.43, 0.49]	[-0.63, 0.50]	[-0.30, 0.50]	[-0.36, 0.64]	[-0.50, 2.23]	[-0.49, 2.86]
Other	0.915[c]	0.846[c]	0.390[c]	0.355[b]	0.811[a]	1.208[b]
	[0.62, 1.21]	[0.49, 1.20]	[0.13, 0.65]	[0.04, 0.67]	[-0.07, 1.70]	[0.15, 2.27]
Vulnerable according to government category and require shielding (1 = yes, 0 = no)	1.087[c]	1.096[c]	0.909[c]	0.945[c]	4.281[c]	3.513[c]

	[0.83, 1.34]	[0.76, 1.43]	[0.68, 1.13]	[0.65, 1.24]	[3.51, 5.05]	[2.52, 4.50]
Experienced coronavirus (1 = yes, 0 = no)	0.324[c]	0.220[b]	0.237[c]	0.181[b]	0.410[a]	0.547[b]
	[0.18, 0.47]	[0.05, 0.39]	[0.11, 0.36]	[0.03, 0.33]	[-0.01, 0.83]	[0.05, 1.05]
Pre-existing mental health condition (1 = yes, 0 = no)	3.447[c]	3.256[c]	3.158[c]	3.091[c]	8.608[c]	8.227[c]
	[3.26, 3.63]	[3.04, 3.47]	[3.00, 3.32]	[2.90, 3.28]	[8.06, 9.16]	[7.60, 8.86]
Drinking alcohol (1 = yes, 0 = no)	0.251[c]	-0.082	0.234[c]	-0.101	0.410	-0.277
	[0.08, 0.42]	[-0.30, 0.13]	[0.08, 0.38]	[-0.29, 0.09]	[-0.10, 0.92]	[-0.91, 0.36]
Taking drug (1 = yes, 0 = no)	0.794[c]	1.303[c]	0.725[c]	0.729[c]	2.262[c]	2.527[c]
	[0.48, 1.11]	[0.76, 1.84]	[0.45, 1.00]	[0.25, 1.21]	[1.33, 3.19]	[0.95, 4.11]
Ever experienced suicidal thoughts (1 = yes, 0 = no)	3.101[c]	2.976[c]	1.623[c]	1.503[c]	6.054[c]	5.812[c]
	[2.95, 3.25]	[2.80, 3.15]	[1.49, 1.75]	[1.35, 1.66]	[5.61, 6.50]	[5.30, 6.32]
Mental health support from (base: No support)	0.000	0.000	0.000	0.000	0.000	0.000
Health service provider	0.134	0.245[a]	-0.052	-0.021	0.008	-0.030
	[-0.11, 0.37]	[-0.03, 0.52]	[-0.26, 0.16]	[-0.26, 0.22]	[-0.71, 0.72]	[-0.85, 0.79]
Other	1.072[c]	1.269[c]	0.521[c]	0.666[c]	3.042[c]	3.542[c]
	[0.77, 1.38]	[0.91, 1.63]	[0.25, 0.79]	[0.35, 0.98]	[2.14, 3.95]	[2.49, 4.59]
Constant	7.050[c]	7.213[c]	4.651[c]	4.590[c]	16.577[c]	16.791[c]
	[6.73, 7.37]	[6.69, 7.73]	[4.37, 4.93]	[4.13, 5.05]	[15.62, 17.54]	[15.26, 18.32]
Observations	28560	21077	28710	21202	26913	19785
Adjusted R^2	0.279	0.261	0.214	0.203	0.180	0.172

[a]$P < 0.10$.
[b]$P < 0.05$.
[c]$P < 0.01$.
[1]See Table 3 for dates of first lock down period.
95% confidence intervals are in brackets. PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7; COVID-19: Coronavirus disease 2019.

In both regression tables, lockdown withdraw dummy in RDD specification showed that lockdown withdraw had statistical and significant effects on mental health indices, which supported the findings of our previous paper that showed that lockdown increased participants mental health scores, or worsened participant's mental health[8].

In both regression tables, compared to the youngest age group (under 25), other age groups had lower scores on the mental health scales, meaning better mental health. Non-White participants reported better mental health than White participants, in most cases. Non-Christians reported better mental health than Christians in both rounds. In both rounds, higher educated participants had better mental health than the lowest educated group.

Heterogenous effects

To demonstrate heterogeneous effects of cumulative COVID cases on mental health scores for different countries, we ran regressions without RDD specification for each country separately, but we included all characteristics used in previous regressions. RDD specification was only applicable to United Kingdom data.

For China (Hong Kong), cumulative COVID cases was extremely low, and therefore, the coefficients of daily cumulative COVID cases were extremely high. Similarly high and low coefficients in different countries depended on scales of cumulative COVID cases in the relevant countries.

Most countries did not show any significant effects. United Kingdom had very good distribution of survey respondents over a long period of time. Therefore, regression results for United Kingdom are more reliable than others. The results are statistically positive in both rounds in the United Kingdom. The first round in the United Kingdom showed statistically and significantly higher positive results. As we have seen in Table 4, such significance vanishes with the inclusion of RDD specification.

DISCUSSION

Using repeated cross sectional survey data of eight country groups and cumulative COVID-19 cases of same countries from Microsoft AZURE, this study found that the daily cumulative COVID-19 cases had a statistically significant effect on

Table 5 Ordinary least squares regression of mental health scores on cumulative coronavirus disease 2019 case, lockdown, and individual characteristics (survey round 2)

	PHQ-9		GAD-7		IES-R	
	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Daily cumulative COVID-19 case/1000000	0.195[c]	0.433[c]	0.129[c]	0.557[c]	0.454[c]	1.265[c]
	[0.18, 0.21]	[0.23, 0.63]	[0.11, 0.15]	[0.38, 0.74]	[0.40, 0.51]	[0.67, 1.86]
Dummy for second lockdown withdraw		-0.507[c]		-0.343[b]		-1.077[b]
		[-0.83, -0.18]		[-0.63, -0.05]		[-2.04, -0.11]
Dummy for second lockdown withdraw[1] (date-second lockdown withdraw date)		-0.034[c]		-0.038[c]		-0.104[c]
		[-0.06, -0.01]		[-0.06, -0.02]		[-0.18, -0.03]
Date-second lockdown withdraw date		0.013		-0.002		0.034
		[-0.01, 0.03]		[-0.02, 0.02]		[-0.03, 0.10]
Healthcare professional (1 = yes, 0 = no)	-0.693[c]	-0.747[c]	-0.540[c]	-0.587[c]	-2.325[c]	-2.551[c]
	[-0.80, -0.58]	[-0.86, -0.63]	[-0.64, -0.44]	[-0.69, -0.48]	[-2.65, -2.00]	[-2.89, -2.21]
Age (base: Below 25)						
25-44	-1.147[c]	-1.339[c]	-0.333[c]	-0.445[c]	-1.043[c]	-0.715[b]
	[-1.34, -0.96]	[-1.55, -1.13]	[-0.50, -0.16]	[-0.63, -0.26]	[-1.60, -0.49]	[-1.33, -0.10]
45-54	-2.059[c]	-2.245[c]	-1.310[c]	-1.421[c]	-2.263[c]	-1.750[c]
	[-2.27, -1.85]	[-2.47, -2.02]	[-1.50, -1.12]	[-1.63, -1.22]	[-2.88, -1.65]	[-2.42, -1.08]
55 and over	-3.455[c]	-3.639[c]	-2.424[c]	-2.521[c]	-4.792[c]	-4.223[c]
	[-3.66, -3.25]	[-3.87, -3.41]	[-2.61, -2.24]	[-2.72, -2.32]	[-5.40, -4.18]	[-4.89, -3.55]
White (1 = yes, 0 = no)	-0.291[c]	-0.243[c]	-0.326[c]	-0.249[c]	-2.114[c]	-1.667[c]
	[-0.42, -0.16]	[-0.38, -0.11]	[-0.44, -0.21]	[-0.37, -0.13]	[-2.49, -1.74]	[-2.07, -1.27]
Christian (1 = yes, 0 = no)	-0.017	0.018	0.174[c]	0.183[c]	0.752[c]	0.795[c]
	[-0.11, 0.08]	[-0.08, 0.12]	[0.09, 0.26]	[0.10, 0.27]	[0.47, 1.03]	[0.50, 1.09]
Male (1 = yes, 0 = no)	-1.470[c]	-1.476[c]	-1.491[c]	-1.523[c]	-4.418[c]	-4.798[c]
	[-1.57, -1.37]	[-1.58, -1.37]	[-1.58, -1.40]	[-1.62, -1.43]	[-4.72, -4.12]	[-5.12, -4.48]
Attended university (1 = yes, 0 = no)	-0.699[c]	0.000	-0.543[c]	0.000	-0.174	0.000
	[-0.96, -0.43]	[0.00, 0.00]	[-0.78, -0.31]	[0.00, 0.00]	[-0.95, 0.60]	[0.00, 0.00]
Own home (1 = yes, 0 = no)	-1.328[c]	-1.391[c]	-0.899[c]	-0.957[c]	-2.985[c]	-3.338[c]
	[-1.44, -1.22]	[-1.51, -1.27]	[-1.00, -0.80]	[-1.06, -0.85]	[-3.32, -2.65]	[-3.69, -2.99]
Vulnerable according to government category and require shielding (1 = yes, 0 = no)	1.355[c]	1.393[c]	1.083[c]	1.124[c]	3.932[c]	3.929[c]
	[1.25, 1.46]	[1.28, 1.51]	[0.99, 1.18]	[1.02, 1.23]	[3.61, 4.26]	[3.59, 4.27]
Experienced coronavirus (1 = yes, 0 = no)	0.747[c]	0.715[c]	0.566[c]	0.535[c]	2.601[c]	2.398[c]
	[0.64, 0.85]	[0.61, 0.82]	[0.47, 0.66]	[0.44, 0.63]	[2.30, 2.91]	[2.08, 2.71]
Pre-existing mental health condition (1 = yes, 0 = no)	2.808[c]	2.745[c]	2.278[c]	2.266[c]	7.150[c]	7.160[c]
	[2.62, 2.99]	[2.55, 2.94]	[2.11, 2.44]	[2.10, 2.44]	[6.60, 7.70]	[6.60, 7.73]
Drinking alcohol (1 = yes, 0 = no)	2.300[c]	2.506[c]	1.714[c]	1.875[c]	5.976[c]	6.400[c]
	[2.17, 2.43]	[2.36, 2.65]	[1.60, 1.83]	[1.75, 2.00]	[5.59, 6.37]	[5.98, 6.82]
Taking drug (1 = yes, 0 = no)	1.232[c]	1.359[c]	0.539[c]	0.562[c]	3.126[c]	3.270[c]
	[1.01, 1.46]	[1.10, 1.62]	[0.34, 0.74]	[0.33, 0.79]	[2.46, 3.79]	[2.51, 4.03]
Ever experienced suicidal thoughts (1 = yes, 0 = no)	4.405[c]	4.379[c]	2.749[c]	2.716[c]	9.625[c]	9.747[c]

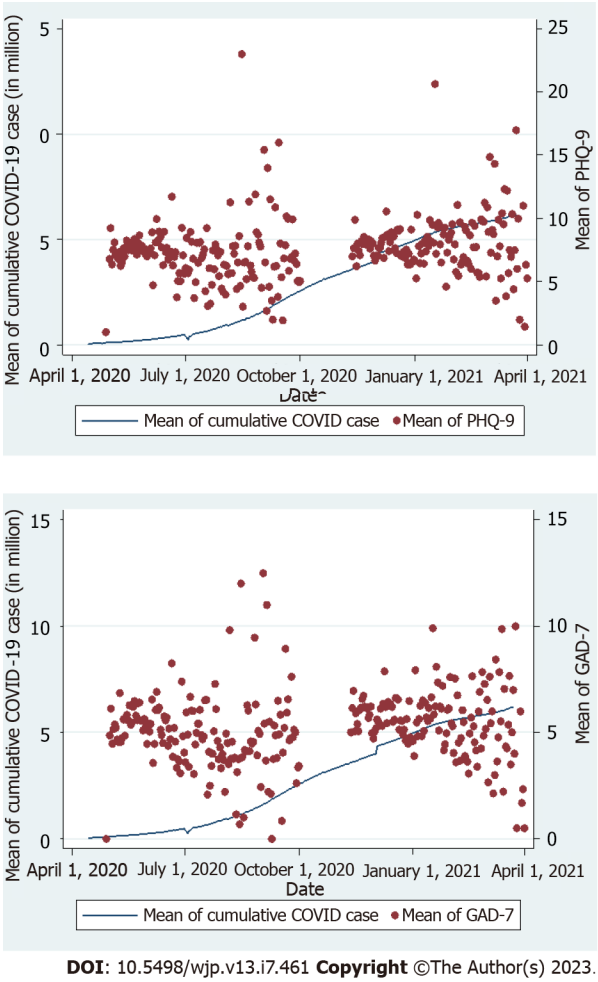
	[4.29, 4.52]	[4.26, 4.49]	[2.65, 2.85]	[2.61, 2.82]	[9.30, 9.95]	[9.41, 10.09]
Mental health support from (base: No support)						
Health service provider	0.322[c]	0.342[c]	-0.024	-0.051	-0.124	-0.288
	[0.10, 0.55]	[0.11, 0.57]	[-0.22, 0.17]	[-0.26, 0.15]	[-0.79, 0.54]	[-0.97, 0.39]
Other	1.041[c]	1.300[c]	0.686[c]	0.854[c]	2.979[c]	3.572[c]
	[0.78, 1.31]	[1.02, 1.58]	[0.45, 0.92]	[0.61, 1.10]	[2.20, 3.76]	[2.75, 4.40]
Constant	8.201[c]	8.292[c]	6.023[c]	5.496[c]	17.577[c]	16.168[c]
	[7.98, 8.42]	[7.84, 8.74]	[5.83, 6.22]	[5.10, 5.90]	[16.94, 18.21]	[14.84, 17.50]
Observations	62938	57985	63545	58547	58966	54202
Adjusted R^2	0.315	0.318	0.228	0.230	0.222	0.228

[b]$P < 0.05$.

[c]$P < 0.01$.

[1]See Table 3 for dates of first lock down period.

95% confidence intervals are in brackets. PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7; COVID-19: Coronavirus disease 2019.



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Figure 3 The association between mental health scores and coronavirus disease 2019 case. A: Mean of patient health questionnaire-9; B: Mean of impact of events scale-revised; C: Mean of generalized anxiety disorder-7. PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7; COVID-19: Coronavirus disease 2019.

three mental health scale indices: Depression, anxiety, and trauma. Ordinary least squares regression results with RDD specification to control for lockdown effects confirms the results. The results are dominated by data in the United Kingdom, which has the largest number of respondents with wider distribution over time. The study findings imply that

participants' mental health worsened with high cumulative COVID-19 cases. Daily cases did not show any impact on mental health scores of participants. The study also highlights other important demographic information and differences due to impact of the COVID-19 pandemic on different countries' participants.

These findings are understandable, considering the significant impact of COVID-19 pandemic on the lives of people across the globe and similar results from other data. Evidence from the Centre for Disease Control and Prevention has shown that fear and stress related to the COVID-19 has led to symptomatology, including change in sleep and eating patterns, worsening of premorbid psychiatric conditions, and increased use of substances (*e.g.*, alcohol, tobacco, drugs), which add to the mental health burden[21]. Quadros *et al*[22] conducted a scoping review and concluded that females, younger adults, urban residents, divorcees, healthcare workers, those in quarantine settings, those in suspicion of being infected, and those with mental health problems, were found to be at an increased risk of COVID-19-related fear[22].

High cumulative COVID-19 cases not only presented a fear of infection and mortality, especially in vulnerable groups, but also impacted on education, jobs, ability to socialize, relationships, loneliness, and other socio-cultural and socioeconomic variables. Most studies have shown an impact on young people's mental health as does this study and the same study in United Kingdom participants has shown an increase in suicidal thoughts[23,24]. High cumulative cases additionally meant the implementation of public health interventions and lockdowns restricting activities. Our findings from the United Kingdom data of the same study demonstrate the positive association of lockdown relaxation and face covering policies on the mental health of participants evidencing the impact of these interventions on mental health of populations as also demonstrated by the international data in this study[9].

These results add to existing global evidence of the psychological impact of the COVID-19 pandemic and previous studies that have demonstrated the adverse impact of population shocks on population mental health[25-27]. A systematic review of data published between January 2020 to January 2021 during the COVID-19 pandemic found that daily SARS-CoV-2 infection rates and reductions in human mobility were associated with increased prevalence of major depressive disorder[28]. These findings have been confirmed by the WHO[3].

In our study, participants from Hong Kong, India and Ukraine had lower mental health scores than other countries' participants. It is not possible to make conclusions on these findings as the number of participants were small and there would be an element of time of participation in the survey.

Different countries had their case number surges and lockdowns at different times during the pandemic. Similarly different countries followed a different trajectory depending on their populations, readiness to respond, political, cultural, financial, and technical landscape. As an example, Ukraine underwent change in ministers three times during the pandemic. There were other determinants of response to the pandemic including levels of awareness, stigma, fear in the early phases of pandemic and attributions to the illness based on cultural explanations[11].

Since the COVID-19 pandemic, the need for mental health support services has increased significantly[29]. This has been particularly difficult due to isolation and distancing measures, causing a physical barrier to help-seeking and treatment implementation[29,30]. Mental health rehabilitation interventions aim to increase social skills and teach coping strategies through training and increased social interactions[29]. This can help individuals with various mental health conditions but is especially useful for those with anxiety or depression[30]. Social and peer support is an integral part of mental health rehabilitation, yet the isolating protection measures of the COVID-19 pandemic pose a barrier[30].

Measures, such as regular testing or online programmes, are some actions which help to overcome these unprecedented circumstances[30,31]. Many organisations and facilities moved their services online in order to provide continuous psychological support for their clients[30,31]. This will ensure that services can continue to operate whilst controlling the spread of the pandemic[31]. The United Kingdom government has published a COVID-19 Mental Health and Wellbeing Recovery Action Plan to accommodate for mental health interventions throughout and post-pandemic [32]. The plan outlines various measures including support for young people, assistance within the employment sector, and accessible and widely available support for frontline healthcare workers[32]. Whilst mental health has always been a pressing matter, the pandemic has amplified its prevalence and affects across all demographic groups[32]. As there were rigid isolation regulations in place, this made the imple-mentation of support difficult so organisations had to be innovative with the ways in which they would continue to assist clients[33]. Likewise, the pandemic also helped to highlight vulnerable groups, leading to the implementation of better support strategies and frameworks for these groups [33].

The results of this study should be interpreted considering its limitations. The timing of the study was such that most countries were in different phases of the pandemic. To conduct a study in that unusual environment meant that some may not consider this a cross sectional study in the epidemiological sense, and it could be difficult to judge the true population prevalence and make international comparisons. For this reason, we have explained the landscape of the different countries separately. This limitation could not have been avoided given the unpredictable nature of the spread of virus, even if confined parameters had been used. Additionally, where many cultural adaptations were made to account for the differences in the countries, it may still be difficult to draw conclusions about the differences in these populations which might be attributable to COVID as the measures are all taken after the onset of the pandemic. Another limitation concerning cumulative cases is that in many low and middle income countries, public health infrastructures and disease notification are very different to those used in high income countries, meaning that the potential for under-ascertainment of cases is much higher. The study has a high number of missing cases and non-random selection of participants are further limitations. In some participating centres the numbers are small. Many surveys were in circulation during this time in all the participating countries, especially during the second round, which may have affected the participation in the survey. Most studies of similar kind have reported small numbers.

CONCLUSION

The results from the current study add to developing evidence of the psychological impact of COVID-19, especially daily cumulative cases on three mental health indices. Building a database of evidence will allow for future planning of pandemics, particularly the impact on mental health of populations and the cultural differences.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic had a huge effect on mental health across the globe. As the pandemic developed over time, international rates of mental health conditions increased. It would be insightful to explore how the increasing cases of COVID-19 impacted mental health throughout the pandemic.

Research motivation

Exploring the impacts of COVID-19 on mental health with help construct a better understanding of the current mental health situation across the globe. It will also help to inform pandemic preparedness policies around mental health services.

Research objectives

This study aimed to explore the psychological implications of the increasing COVID-19 case throughout the pandemic across various countries.

Research methods

A repeated, cross-sectional online international survey of adults was carried out in 10 countries. Five standardised psychological measures were included to explore the psychological impact of cumulative COVID-19 cases. This was carried out at two timepoints in all countries, aside from the United Kingdom which collected data at 3 timepoints.

Research results

There were two rounds of the online survey in eight country groups with 42866 participants recruited in Round 1 and 92260 recruited in Round 2. This study found that the daily cumulative COVID-19 cases had a statistically significant effect on three depression, anxiety, and trauma. Trauma scores were higher across all countries compared to those for anxiety and depression. All scores increased in Round 2 in all countries.

Research conclusions

Considering the significant impact of COVID-19, understanding the effects will enable for adequate services and support to be put in place. This evidence dataset will also help inform the policies and strategies for pandemic preparedness.

Research perspectives

COVID-19 has had enduring effects in all aspects of life including physical and mental health.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Role of comprehensive geriatric assessment in screening for mild cognitive disorders

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Abstract

BACKGROUND

The role of comprehensive geriatric assessment (CGA) in screening for mild cognitive disorders was not known.

AIM

To evaluate the role of CGA in screening for mild cognitive disorders.

METHODS

A total of 100 elderly people who underwent health examinations in our hospital and community between January 2020 and December 2021 were included for analysis. Using Petersen as the diagnostic gold standard, healthy individuals were included in the control group and patients with mild cognitive impairment were assigned to the study group. The correlation between the cognitive function of the patients and their baseline clinical profiles was analyzed. Patients' Montreal Cognitive Assessment (MoCA) and CGA screening results were compared, and the sensitivity and specificity were calculated to assess the screening role of CGA.

RESULTS

CGA assessment yielded higher diagnostic accuracy than MoCA. The results of the multivariate regression analysis showed no correlation of gender, age, body mass index and literacy with cognitive function. Patients with mild cognitive impairment obtained significantly lower MoCA scores than healthy individuals ($P < 0.05$). In the CGA scale, patients with mild cognitive impairment showed significantly lower Mini-mental State Examination, Miniature Nutritional Assessment and Berg Balance Scale scores, and higher Activity of Daily Living, Instrumental Activities of Daily Living Scale and Frailty Screening Inventory scores than healthy individuals ($P < 0.05$), whereas the other assessment scales showed no significant differences ($P > 0.05$). The CGA provides higher diagnostic sensitivity and specificity than the MoCA ($P < 0.05$).

CONCLUSION
CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

Key Words: Comprehensive geriatric assessment; Mild cognitive impairment; Screening; Montreal Cognitive Assessment; Sensitivity; Specificity

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Core Tip: Comprehensive geriatric assessment allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

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INTRODUCTION

Mild cognitive impairment (MCI) is the transitional state between normal aging and mild dementia and is an early stage of dementia[1,2]. People with MCI present with memory impairment that exceeds the allowable range for their age and culture. However, they experience normal social work or daily functioning and do not meet the diagnostic criteria for dementia. Evidence suggests that within the following 2-5 years, mild cognitive impairment is associated with a higher risk of developing dementia compared to age-appropriate non-mild cognitive impairment, which may be attributable to multiple diseases[3]. There is a prevalence of mild cognitive impairment of over 15% in people over 65 years of age, with 10%-15% of the population deteriorating to Alzheimer's disease within one year per year, whereas the prevalence in the normal population averages only 1%-2%. Therefore, enhanced detection, intervention, or delay of the onset of cognitive impairment in mild cognitive impairment at an early clinical stage is necessary[4,5]. Timely diagnosis of patients with mild cognitive impairment is a prerequisite for treatment and can efficiently mitigate the progression of the disease. Screening for mild cognitive impairment is normally performed using the Montreal cognitive assessment (MoCA)[6,7], a scale that references the cognitive elements and scores of the Mini-mental State Examination (MMSE) to assess mild cognitive impairment[8]. However, the results of studies related to the cut-off point, sensitivity and specificity of the scale vary considerably. Comprehensive geriatric assessment (CGA)[9] is a multidisciplinary approach that assesses the physical health, functional status, mental health and social-environmental status of older people[10]. CGA can facilitate timely treatment, slow down the disease process and reduce dementia through multidimensional analysis of MCI[11,12]. To this end, the current research was performed to evaluate the role of CGA in screening for mild cognitive disorders.

MATERIALS AND METHODS

Case selection

A total of 100 elderly people who underwent health examinations in our hospital and community between January 2020 and December 2021 were included for analysis. Written informed consent was obtained from all patients in this study.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with objective signs of impairment in one or more areas of cognitive function; (2) patients met the relevant diagnostic criteria in the Diagnosis and Treatment of Mild Cognitive Impairment; and (3) clinical information was complete, with no restriction on gender, and age no less than 60 years.

Exclusion criteria: (1) Patients met the diagnostic criteria for clinical dementia; (2) physical organ disability, including vision and hearing; and (3) inability to cooperate with the completion of this study for psychiatric reasons.

Methods

Using Petersen as the diagnostic gold standard, healthy individuals were included in the control group and patients with mild cognitive impairment were assigned to the study group. The correlation between the cognitive function of the patients and their baseline clinical profiles was analyzed. Patients' MoCA and CGA screening results were compared, and the sensitivity and specificity were calculated to assess the screening role of CGA.

Outcome measures

Petersen diagnosis: The patient reported memory loss for no less than 3 mo, which was confirmed by others; age-incompatible objective memory decline, with overall normal cognitive function and a Geriatric Depression Scale (GDS) score of 2-3; patients had essentially normal activities of daily living and an Activity of Daily Living (ADL) score no higher than 18; patients did not meet the US NIA-AA dementia diagnostic criteria for dementia, with a CDR score = 0.5.

MoCA: The Chinese version of the MoCA scale developed by Peking Union Medical College Hospital and Professor Nasreddine was used for assessment. The scale has a total score of 30 and includes eight cognitive domains, namely time, positional orientation, language, calculation, memory and delayed memory, visuospatial ability, executive function, attention and abstract thinking. Scores are proportional to cognitive functioning, with scores below 26 indicating impaired cognitive functioning[13].

CGA: The CGA assesses the cognitive status of patients through the General Medical Assessment, Physical Functioning Assessment, Psychosocial Assessment, Social Health Assessment, Environmental Assessment, Quality of Life Assessment and Assessment of Common Symptoms or Problems in Older Adults. It includes the GDS, Geriatric Anxiety Inventory (GAI), MMSE, Miniature Nutritional Assessment (MNA), ADL, Instrumental Activities of Daily Living Scale (IADL), Frailty Screening Inventory (FRAIL), Berg Balance Scale (BBS), Falls Risk Factor Assessment (FRAF), and PAGAR. GDS, GAI, MMSE, MNA, BBS, FRAF, and PAGAR were proportional to the CGA score, and ADL, IADL, and FRAIL were inversely proportional to the CGA score.

Statistical analysis

SPSS 26.0 was used for data analyses. Measurement data were expressed as mean ± SD and tested using independent samples *t*-test. Count data were expressed as number of cases (%) and tested using χ^2 test. Pearson correlation analysis was applied for multiple regression analysis. Statistical significance was indicated by $P < 0.05$.

RESULTS

Screening results

Petersen diagnosed 62 healthy individuals as controls and 38 patients with mild cognitive impairment as the study group. The MoCA diagnosed 30 cases of healthy individuals and 38 cases of patients with mild cognitive impairment, while the CGA assessment showed 58 cases of healthy individuals and 36 cases of patients with mild cognitive impairment. CGA assessment yielded higher diagnostic accuracy than MoCA (Table 1 and Table 2).

Baseline patient profiles

The control group consisted of 41 males and 21 females, aged 62-80 (71.84 ± 7.21) years, with a body mass index (BMI) of 20-26 (24.18 ± 2.11) kg/m^2. There were 5 cases of illiteracy, 18 cases with an education level of primary school, 25 cases of junior high school, and 14 cases of high school and above. The study group consisted of 25 males and 13 females, aged 61-79 (71.52 ± 7.36) years, with a BMI of 20-26 (24.21 ± 2.07) kg/m^2. There were 2 cases of illiteracy, 11 cases with an education level of primary school, 16 cases of junior high school, and 9 cases of high school and above. The two arms were well-balanced in terms of baseline patient profiles ($P > 0.05$, Table 3).

Correlation

The results of the multivariate regression analysis showed no correlation of gender, age, body mass index and literacy with cognitive function ($P > 0.05$, Table 4).

MoCA scores

MoCA score in the control group was 26.88 ± 2.14 and the MoCA score in the study group was 20.86 ± 2.56. Patients with mild cognitive impairment obtained significantly lower MoCA scores than healthy individuals ($P < 0.05$, Table 5).

CGA scores

In the CGA scale, patients with mild cognitive impairment showed significantly lower MMSE, MNA and BBS scores, and higher ADL, IADL and FRAIL scores than healthy individuals ($P < 0.05$), whereas the other assessment scales showed no significant differences ($P > 0.05$) (Table 6).

Application value of CGA vs MoCA

The sensitivity and specificity of MoCA was 0.761 and 0.714, while the sensitivity and specificity of CGA was 0.882 and 0.964. The CGA provides higher diagnostic sensitivity and specificity than the MoCA ($P < 0.05$) (Table 7).

DISCUSSION

Cognitive impairment can affect learning, memory, social functioning, language, visuospatial function, and attention, and severe cognitive impairment can lead to dementia. Statistics show that 5%-10% of people with mild cognitive impairment

Table 1 Montreal cognitive assessment results

MoCA results	Study group	Control group
Normal	30	7
Mild cognitive impairment	8	55
Total	38	62

MoCA: Montreal cognitive assessment.

Table 2 Comprehensive geriatric assessment results

CGA results	Study group	Control group
Mild cognitive impairment	36	4
Normal	2	58
Total	38	62

CGA: Comprehensive geriatric assessment.

Table 3 Baseline patient profiles

	Control group, *n* = 62	Study group, *n* = 38	*t* value	*P* value
Sex				
Male	41	25	-	-
Female	21	13	-	-
Age (yr) (mean)	62-80 (71.84 ± 7.21)	61-79 (71.52 ± 7.36)	0.214	0.831
BMI (kg/m^2) (mean)	20-26 (24.18 ± 2.11)	20-26 (24.21 ± 2.07)	0.070	0.944
Education level				
Illiterate	5	2	-	-
Primary school	18	11	-	-
Junior high school	25	16	-	-
High school and above	14	9	-	-

BMI: Body mass index.

Table 4 Correlation of baseline profiles and cognitive function

	B	SE	B'	*t* value	*P* value
Sex	-1.612	2.705	-0.079	-0.521	0.511
Age	-0.154	0.088	-0.227	1.794	0.094
BMI	0.012	0.069	0.034	0.314	0.807
Education level	0.714	0.763	0.185	0.894	0.352

BMI: Body mass index.

develop dementia each year, which is higher than the 1%-2% annual prevalence in the general population. Nearly 50 million people worldwide suffered from dementia in 2016, and its prevalence has been increasing[14]. The aging population and the increasing prevalence of dementia are the primary contributors to the expected increase in the cost of dementia. Few clinically effective medications are available for the treatment of cognitive impairment. However, studies have shown that 30%-50% of patients initially diagnosed with mild cognitive impairment recover to a normal cognitive

Table 5 Montreal cognitive assessment scores

	Control group	Study group	*t* value	*P* value
n	62	38	-	-
MoCA scores	26.88 ± 2.14	20.86 ± 2.56	12.663	< 0.001

MoCA: Montreal cognitive assessment.

Table 6 Comprehensive geriatric assessment scores

	Control group, *n* = 62	Study group, *n* = 38	*t* value	*P* value
GDS	9.61 ± 3.98	10.05 ± 3.88	0.542	0.589
GAI	3.62 ± 3.25	3.44 ± 3.18	0.271	0.787
MMSE	28.85 ± 1.85	26.05 ± 1.27	8.212	< 0.001
MNA	22.51 ± 4.14	19.14 ± 3.52	4.176	< 0.001
ADL	17.25 ± 2.62	19.58 ± 2.14	4.616	< 0.001
IADL	10.52 ± 3.51	12.88 ± 3.54	3.253	0.002
FRAIL	1.25 ± 0.25	1.89 ± 0.57	7.728	< 0.001
BBS	44.52 ± 7.98	39.21 ± 8.11	3.210	0.002
FRAF	2.62 ± 1.25	2.68 ± 1.31	0.229	0.819
PAGAR	8.29 ± 2.58	8.33 ± 2.49	0.076	0.940

CGA: Comprehensive geriatric assessment; GDS: Geriatric depression scale; GAI: Geriatric anxiety inventory; MMSE: Mini-mental state examination; MNA: Miniature nutritional assessment; ADL: Activity of daily living scale; IADL: Instrumental activities of daily living scale; FRAIL: Frailty screening inventory; BBS: Berg balance scale; FRAF: Falls risk factor assessment.

Table 7 Sensitivity and specificity of Montreal cognitive assessment and comprehensive geriatric assessment

	MoCA	CGA
Sensitivity	0.761	0.882
Specificity	0.714	0.964

MoCA: Montreal cognitive assessment; CGA: Comprehensive geriatric assessment.

level during postoperative care. Therefore, timely screening and prevention will contribute to improving the standard of living of patients and reducing the family, social and economic burden[15,16]. Patients with mild cognitive impairment show no typical clinical manifestations in the early stages, which poses difficulties in the clinical diagnosis of the disease and is detrimental to the early identification and targeted treatment of the condition.

The MoCA is an assessment scale for mild cognitive impairment developed by Canadian scientists based on clinical experience and with reference to the cognitive elements and scores of the MMSE[17,18]. In the present study, patients with mild cognitive impairment showed significantly lower MMSE, MNA, and BBS scores, and higher ADL, IADL and FRAIL scores than healthy individuals, whereas the other assessment scales showed no significant differences, and the CGA provides higher diagnostic sensitivity and specificity than the MoCA, which was consistent with the findings of previous studies. It has been reported that the relative risk of conversion to dementia in those with cognitive abnormalities is 6.4 times higher than in those with normal cognition. Mild cognitive impairment is an early manifestation of dementia, and the MMSE is a scale that has been used to assess cognitive ability. It has been proposed that the dietary patterns of patients have implications for future perceptions in life, and that most older people require treatment for nutritional deficiencies to prevent cognitive decline. As a result, greater emphasis should be placed on screening for nutritional status in patients with mild cognitive impairment to ensure adequate nutritional support. In 2013, the International Academy of Nutrition and Aging and the International Association of Geriatrics introduced the concept of 'cognitive deprivation', linking cognition to deprivation. The present study also found that the results of the multiple regression analysis showed that gender, age, BMI and literacy were not correlated with cognitive function. However, this is inconsistent in previous studies and may be the result of the large variation in sample size from one study to another, with increased sample size contributing to the analysis of cognitive function factors.

The MoCA scale focuses on a single disease and fails to fully address the healthcare needs of older people. CGA was originally proposed by British scientists in 1946 as an intervention to comprehensively assess the illness, physical ability, cognitive, psychological, social and economic status of elderly patients at multiple levels, so as to comprehensively assess older people with a function-oriented approach during the recovery phase of chronic disease to guide treatment and health maintenance. Currently, it is widely used to determine the level of health functioning of older people and is recognized for its effectiveness in improving diagnosis, prognosis and quality of life of patients. Nevertheless, no consensus has been reached on the content of their specific assessments. Heterogeneity in the size of different research institutions precludes the comparison of different findings, for which the identification of standardized comprehensive CGA assessments for older people is an effective approach. However, a large body of evidence is required[19,20].

Limitations

Research suggests that all people over the age of 70 years ought to undergo annual subjective or objective cognitive testing with their healthcare provider. However, this has significantly increased the workload of medical staff, resulting in high human costs. This could be improved in the future through the development of a fee schedule for comprehensive assessments, including health insurance, changes to the writing of health records, the addition of a "comprehensive assessment and diagnosis for older people" and the conversion of different assessment scales into electronic health records. Limitations of the current study include the risk of bias due to insufficient sample size and lack of sample diversity. Future studies will expand the sample to further improve the protocol and provide more references for future relevant diagnostic treatments.

CONCLUSION

CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

ARTICLE HIGHLIGHTS

Research background

Comprehensive geriatric assessment (CGA) is a multidisciplinary approach that assesses the physical health, functional status, mental health and social-environmental status of older people. CGA can facilitate timely treatment, slow down the disease process and reduce dementia through multidimensional analysis of Mild cognitive impairment.

Research motivation

This study found that CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention.

Research objectives

This study was conducted to evaluate the role of comprehensive geriatric assessment in screening for mild cognitive disorders.

Research methods

Using Petersen as the diagnostic gold standard, healthy individuals were included in the control group and patients with mild cognitive impairment were assigned to the study group. The correlation between the cognitive function of the patients and their baseline clinical profiles was analysed. Patients' Montreal Cognitive Assessment (MoCA) and CGA screening results were compared, and the sensitivity and specificity were calculated to assess the screening role of CGA.

Research results

CGA assessment yielded higher diagnostic accuracy than MoCA. The results of the multivariate regression analysis showed no correlation of gender, age, body mass index and literacy with cognitive function. Patients with mild cognitive impairment obtained significantly lower MoCA scores than healthy individuals. In the CGA scale, patients with mild cognitive impairment showed significantly lower Mini-mental State Examination, Miniature Nutritional Assessment and Berg Balance Scale scores, and higher Activity of Daily Living, Instrumental Activities of Daily Living Scale and FRAIL scores than healthy individuals. The CGA provides higher diagnostic sensitivity and specificity than the MoCA.

Research conclusions

CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

Research perspectives

Future studies will expand the sample to further improve the protocol and provide more references for future relevant diagnostic treatments.

FOOTNOTES

Author contributions: Yu J and Lu SR contributed equally to this work; Wang Z, Yang Y designed the research study; Zhang BS performed the research; Hong K contributed new reagents and analytic tools; Xu Q analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Factors influencing postoperative anxiety and depression following Iodine-131 treatment in patients with differentiated thyroid cancer: A cross-sectional study

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Abstract

BACKGROUND

Differentiated thyroid cancer (DTC) often seriously impacts patients' lives. Radionuclide Iodine-131 (^{131}I) is widely used in treating patients with DTC. However, most patients know little about radionuclide therapy, and the treatment needs to be performed in a special isolation ward, which can cause anxiety and depression.

AIM

To explore anxiety and depression status and their influencing factors after ^{131}I treatment in patients with DTC.

METHODS

A questionnaire survey was conducted among postoperative patients with DTC who received ^{131}I treatment at our hospital from June 2020 to December 2022. General patient data were collected using a self-administered demographic characteristics questionnaire. The self-rating depression scale and self-rating anxiety scale were used to determine whether patients were worried about their symptoms and the degree of anxiety and depression. The patients were categorized into anxiety, non-anxiety, depression, and non-depression groups. Single-variable and multiple-variable analyses were used to determine the risk factors for anxiety and depression in patients with thyroid cancer after surgery.

RESULTS

A total of 144 patients were included in this study. The baseline mean score of self-rating anxiety and depression scales were 50.06 ± 16.10 and 50.96 ± 16.55, respectively. Notably, 48.62% (70/144) had anxiety and 47.22% (68/144) of the

patients had depression. Sex, age, education level, marital status, household income, underlying diseases, and medication compliance significantly differed among groups ($P < 0.05$). Furthermore, multivariate logistic regression analysis showed that education level, per capita monthly household income, and medication compliance level affected anxiety ($P = 0.015$, 0.001, and 0.001 respectively. Patient's sex, marital status, and underlying diseases affected depression ($P = 0.007$, 0.001, and 0.009, respectively).

CONCLUSION

Nursing interventions aiming at reducing the risk of anxiety and depression should target unmarried female patients with low education level, low family income, underlying diseases, and poor adherence to medications.

Key Words: Iodine-131; Thyroid gland; Neoplasms; Anxiety; Depression; Prognosis

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Core Tip: Differentiated thyroid cancer (DTC) seriously impacts the patient's life and induces more adverse emotions. This study investigated anxiety and depression in 144 patients with DTC. Sex, education level, family factors, and basic diseases were the risk factors for anxiety and depression. Better intervention nursing measures can be proposed for clinical practice by observing and proposing indicators that affect patients' mood risk factors and by comparing them with previous studies, thereby reducing the risk of developing anxiety and depression and improving their prognosis.

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INTRODUCTION

Thyroid cancer is a common malignant head and neck tumor, and its incidence has been annually increasing in recent years[1]. According to the International Agency for Research on Cancer, the worldwide incidence of thyroid cancer is approximately 6.7/100000, and the number of new cases in China is 190000 in 2022[2]. Among them, differentiated thyroid cancer (DTC) accounts for approximately 90%. Currently, DTC is treated with a three-step comprehensive treatment approach consisting of surgery, Iodine-131 (^{131}I) treatment and thyroid hormone suppression[3], which can significantly reduce the tumor recurrence rate and improve disease prognosis. However, the complications of tumor surgery and lack of understanding of ^{131}I treatment, especially the fact that ^{131}I treatment is a type of internal radiotherapy, may result in patients experiencing anxiety, fear, depression, and other negative emotions[4]. In clinical practice, several patients with DTC exhibit anxiety or poor mental state before radiotherapy, which leads to poor compliance with radiotherapy and ultimately affects the clinical treatment effect[5]. Therefore, it is crucial to analyze the anxiety status and related influencing factors of patients with thyroid cancer after surgery. This analysis can guide the formulation of clinical preventive nursing strategies and improve patient outcomes. Along those lines, this study aims to explore the anxiety states and associated risk factors in patients with DTC after ^{131}I treatment.

MATERIALS AND METHODS

Patient characteristics

A questionnaire survey was conducted among postoperative patients with DTC who received ^{131}I treatment at our hospital from June 2020 to December 2022.

Inclusion criteria were as follows: Pathological diagnosis of DTC; clinical indications for surgical treatment and completed surgical treatment; age ≥ 18 years; ability to read and independently complete the questionnaire, the patients were informed, cooperated well, and had complete clinical pathological data. Comply with medical advice, regular postoperative review at our hospital.

The exclusion criteria were as follows: Previous or concurrent malignant tumors combined with anxiety; depression; history of dementia; history of drug abuse; alcoholism; failure of the heart, liver, kidney, and other important organs; hearing and language dysfunction; and inability to cooperate.

A total of 144 patients met the inclusion standard. The patients were divided into anxiety, non-anxiety, depression, and non-depression groups based on their reported anxiety or depression status.

General information collection

General patient data, collected using a self-administered demographic characteristics questionnaire, mainly included age, sex, cultural background, marital status, family per capita monthly income, presence or absence of underlying diseases, and medication compliance. At the same time, the anxiety self-rating scales (SAS) and the self-rating depression scale (SDS) were used to evaluate the anxiety and depression of the patients one month after operation.

Anxiety status assessment

Trained healthcare professionals used SAS to assess anxiety in all patients. The SAS includes 20 items, of which 15 are scored positively, and 5 are scored negatively. Twenty entries add up to a total score of 20. The integer part of the total score was multiplied with 1.25 to obtain the standard score. The threshold was set to 50 points based on the Chinese scoring standard. The degree of anxiety was categorized as mild (50–60 points), moderate (60–80), and severe (80–100).

Depression status assessment

SDS was used to evaluate the depression status of the patients. All patients were evaluated by a professional medical staff member who had undergone systematic training. The SDS includes 20 items, and each item was evaluated using a 4-point Likert scale, with a score of 1–4 points. The rough score was obtained by adding the scores of each item (the reverse item is the reverse score); the coarse fraction was multiplied with 1.25 and the integer part was considered as the standard score. The threshold of the standard SDS score was 53 points, and the normal score was 53 points. Depression was classified as mild (53–60 points), moderate (53–60), or severe (90–100).

Statistical Methods

Descriptive analysis, and single-factor and multi-factor analyses were performed. Descriptive analysis was performed on the number of samples and their compositions. The histogram shows the basic characteristics of anxiety and depression. Univariate chi-square tests and single-factor logistic regression analyses were used to evaluate the influencing factors of anxiety and depression. Anxiety and depression (yes = 1; no = 0) were assigned as the dependent variables. All statistical tests were two-sided, with a statistically significant difference of $P < 0.05$. The data obtained were statistically analyzed using SPSS26.0 (IBM SPSS Inc., Chicago, United States).

RESULTS

Survey population

A total of 144 participants were included in this study, comprising 70 men (48.61%) and 74 women (51.39%). Their age was 18–60 (34.81 ± 4.92) years; and education level was 68 (47.22%) above high school, 76 (52.78%) below high school. Table 1 presents additional basic information collected in this study.

Anxiety and depression

The baseline mean scores of SAS and SDS were 50.06 ± 16.10 and 50.96 ± 16.55, respectively. Further, 51.38% (74/144) of the patients were in a non-anxiety state and 48.62% (70/144) were anxious. The proportions of mild, moderate, and severe anxiety were 21.52%, 24.30%, and 2.78%, respectively. Moreover, 52.78% (76/144) of the patients were non-depressive and 47.22% (68/144) experienced depression. The proportions of mild, moderate, and severe depressive loops were 20.83%, 22.92%, and 3.47%, respectively (Table 2).

Influencing factors of anxiety

Single-factor analysis of anxiety symptoms: The results of single factor showed that there were significant differences between the two groups in education level, family monthly average income and medication rule ($P < 0.05$) (Table 3).

Multivariate analysis of anxiety symptoms: Logistic regression analysis was performed with the dependent variable anxiety. Independent variables included age, sex, marital status, educational level, family income, basic diseases, and medication compliance. The detailed variables assignments are listed in Table 4.

Multivariate analysis showed that education level, monthly average family income, and medication compliance were factors influencing patients' possible anxiety ($P < 0.05$; Table 5). Patients with a high educational level were 0.28 times more likely to experience anxiety than that those with a low educational level. Patients with high family income were 0.09 times more likely to experience anxiety than those with low family income. Patients who took medications regularly were 0.03 times more likely to be anxious than those who missed medications occasionally.

Influencing factors of depression

Single-factor analysis of depression: The results of single factor showed that there were significant differences between the two groups in gender, marital status and basic diseases ($P < 0.05$) (Table 6).

Multivariate analysis of depression: Logistic regression analysis was performed with depression as the dependent variable. Independent variables included age, sex, marital status, educational level, family income, basic diseases, and medication compliance. The variables assignments are listed in Table 4.

Table 1 Characteristics of the survey population

Category	Variable	Number of samples	Percentage (%)
Age	< 30	66	45.83
	≥ 30	78	54.17
Sex	Male	70	48.61
	Female	74	51.39
Education	High school or above	68	47.22
	High school and below	76	52.78
Marital status	Have a spouse	69	47.92
	no spouse	75	52.08
Monthly household income	≥ 5000	70	48.61
	< 5000	74	51.39
Underlying medical conditions	Yes	71	49.31
	No	73	50.69
Medication adherence	Regular	67	46.53
	Irregular	77	53.47

Table 2 Overall status of anxiety and depression in patients undergoing ^{131}I treatment after surgery for differentiated thyroid cancer

Category	Normal	Mild	Moderate	Severe
Anxiety	74 (51.39)	31 (21.52)	35 (24.30)	4 (2.78)
Depression	76 (52.78)	30 (20.83)	33 (22.92)	5 (3.47)

Table 3 Single factor analysis of anxiety in survey participants

Category		Anxiety (n = 70)	Non-anxiety (n = 74)	χ^2	P value
Age	≤ 40	31 (44.29)	35 (47.30)	0.131	0.717
	> 40	39 (55.71)	39 (52.70)		
Sex	Male	33 (47.14)	41 (55.40)	0.983	0.321
	Female	37 (52.86)	33 (44.59)		
Education	High school or above	48 (68.57)	20 (27.03)	24.911	0.001
	High school and below	22 (31.43)	54 (72.97)		
Marital status	Have a spouse	38 (54.29)	35 (47.30)	0.703	0.402
	No spouse	32 (45.71)	39 (52.70)		
Monthly household income	≤ 5000	51 (72.86)	19 (25.68)	32.065	0.001
	> 5000	19 (27.14)	55 (74.32)		
Underlying medical conditions	Yes	37 (52.86)	34 (45.95)	0.687	0.407
	No	33 (47.14)	40 (54.05)		
Medication adherence	Irregular	56 (80.00)	11 (14.86)	61.342	0.001
	Regular	14 (20.00)	63 (85.14)		

Logistic multivariate regression analysis showed that the factors influencing depression were sex, marital status, and basic diseases (P < 0.05). Female patients were more likely to have depression than male patients. Patients without a spouse were more likely to experience depression than those with a spouse. Patients with underlying diseases were more likely to have depression than those without. Detailed data analysis is presented in Table 7.

Table 4 Assignments

Category	Assignment
Age	≤ 40 = 1; > 40 = 0
Education	High school or above = 1; High school and below = 0
Sex	Male = 1; Female = 0
Marital status	Have a spouse = 1; No spouse = 0
Monthly household income	> 5000 = 1; ≤ 5000 = 0
Underlying medical conditions	Yes = 1; No = 0
Medication adherence	Regular = 1; Irregular = 0
Anxiety	Anxiety = 1; Non-anxiety = 0
Depression	Depression = 1; Non-depression = 0

Table 5 Multivariate logistic analysis of anxiety in differentiated thyroid cancer patients after ^{131}I treatment and surgery

Factors	β	SE	Wald χ^2 value	*P* value	OR	95%CI
Education	-1.256	0.518	5.872	0.015	0.285	0.103–0.786
Family monthly income	-2.402	0.587	16.719	0.001	0.091	0.029–0.286
Medication compliance	-3.292	0.585	31.617	0.001	0.037	0.012–0.117

SE: Standard error

Table 6 Univariate analysis of the depression in patients with differentiated thyroid cancer after ^{131}I treatment and surgery

Catalog		Depression (*n* = 68)	Non-depression (*n* = 76)	χ^2 value	*P* value
Age	≤ 40	34 (50.00)	32 (42.11)	0.901	0.343
	> 40	34 (50.00)	44 (57.89)		
Sex	Male	27 (39.71)	47 (61.84)	7.040	0.008
	Female	41 (60.29)	29 (38.16)		
Education	High school and below	34 (50.00)	34 (44.74)	0.399	0.528
	High school or above	34 (50.00)	42 (55.26)		
Marital status	Have a spouse	22 (32.35)	51 (67.11)	17.341	0.001
	No spouse	46 (67.65)	25 (32.89)		
Monthly household income	≤ 5000	37 (54.41)	33 (43.42)	1.735	0.188
	> 5000	31 (45.59)	43 (56.58)		
Underlying medical conditions	Yes	44 (64.71)	27 (35.53)	7.614	0.006
	No	24 (35.29)	49 (64.47)		
Medication adherence	Irregular	36 (52.94)	31 (40.79)	2.130	0.144
	Regular	32 (47.06)	45 (59.21)		

DISCUSSION

DTC is a common thyroid gland malignancy that occurs in young and middle-aged women[6]. DTC has a serious impact on the lives of patients and also induces more adverse emotions. Radionuclide ^{131}I has been widely used to treat patients with DTC and has contributed to continuous progress in medical technology in China[7]. However, most patients know little about radionuclide therapy, and the treatment needs to be performed in a special isolation ward, which can easily cause anxiety and depression[8]. Thus, it is important to consider the mental health of patients, which is conducive to better recovery.

Table 7 Multivariate Logistic analysis of depression in differentiated thyroid cancer patients after ^{131}I treatment and surgery

Factors	β	SE	Wald χ^2 value	*P* value	OR	95%CI
Sex	-1.096	0.405	7.323	0.007	0.334	0.151–0.739
Marital status	-1.616	0.401	16.210	0.001	0.199	0.091–0.436
Underlying diseases	-1.027	0.396	6.737	0.009	0.358	0.165–1.038

SE: Standard error; OR: Odds ratio.

The findings of this study showed that 48.61% of patients with DTC exhibited anxiety and 47.22% exhibited depression, one month following their ^{131}I treatment initiation. These elevated percentages could be attributed to patients having concerns about the problems associated with radiation involved in ^{131}I treatment during isolation, due to a limited understanding of ^{131}I treatment. These patients are prone to panic, anxiety, and other serious passive moods, which reduce their compliance with treatment and affect the overall treatment outcomes. Therefore, the assessment of anxiety and depression in patients undergoing ^{131}I treatment facilitates the provision of timely counseling intervention to alleviate these negative emotions, and improve patients' treatment compliance, prognosis, and quality of life[9]. Moreover, these negative emotions in patients with thyroid cancer are reported to be associated to age, educational level, and family income[4,10].

In the present study, the anxiety and depression symptom scores of postoperative patients after ^{131}I treatment were 50.06 ± 16.10 and 50.96 ± 16.55, respectively. It has been reported that the main reasons for the high scores of anxiety and depression were the lack of trust in the professional level of the medical staff, lack of understanding of treatment methods, and concerns regarding recurrence and adverse reactions during surgery, as well as the resulting economic burden[11,12]. The superposition of these factors inadvertently leads to high psychological pressure and stress responses in patients, thereby resulting in anxiety and depression[13].

Further multivariate logistic regression analysis showed that patient's education level, family income, and medication regularity were the independent influencing factors of anxiety. Therefore, our results suggest that patients with a low education level, low family income, and irregular adherence to medication were more prone to anxiety. These findings are consistent with those of Yang *et al*[14] and Tsartsalis *et al*[15]. Possible reasons for these results may include the limited knowledge levels among people with low education levels, less access to disease information, a lack of understanding of important stressors, and a difficulty in effectively reducing stress using corresponding methods. Such patients are sensitive to possible threats caused by diseases and operations and are prone to anxiety and depression[16]. Patients with higher education levels have a stronger learning ability and thorough understanding of medical staff's knowledge and educational status. Patients who are able to actively collect information about the disease and its treatment from books, networks, and other means, are better equipped to reduce the psychological burden and eliminate negative emotions. On the other hand, patients with low education levels require repeated explanations, even through the use audiovisual aids to increase their understanding of their diseases, thereby eliminating the uncertainty of the disease or treatment, and improving their confidence in the healing process[17].

Thyroid cancer requires long-term treatment, which is expensive and increases the economic burden of patients. Therefore, family income has also become an independent risk factor for patients ' concerns. Patients with thyroid cancer with a family monthly income ≤ 5000 yuan have often face financial difficulties. They experience significant psychological pressure because they worry about becoming a burden on their families, and they may feel anxious about being unable to afford the long-term medical expenses. The consequent uncertainty of follow-up treatment can easily lead to negative emotions, such as guilt and anxiety. Indeed, patients from low-income families can choose effective and low-cost drug treatment to reduce their families economic burden[18].

Occasionally missed medications are also a risk factor for anxiety in patients with DTC after surgery. Long-term and occasionally missed medication increases the fear of disease recurrence, resulting in anxiety symptoms. Therefore, family members should ensure that patients take their medications on time.

In the present study, sex, marital status, and underlying diseases were independent risk factors for depression. The incidence of depression was higher in women than that in men, which is consistent with previous studies[19]. This reason may be related to cyclical fluctuations in female endocrine hormone levels[20]. In addition, women now play multiple roles in social responsibility, leading to increased stress in life; they are relatively more sensitive, tend to have more physical and emotional pain, which may lead to a poor prognosis[21]. More attention should be paid to the feelings of female patients, and their symptoms should be actively improved to enhance their quality of life. Studies[19] have shown that marital status is an independent risk factor for depression. Although unmarried patients are accompanied by their parents, they lack active support from their spouses or children, and consequently experience greater loneliness than married patients. On the other hand, patients with spouses can receive family support to reduce their risk of anxiety and depression. Studies[22] have also reported that patients with cancer undergoing long-term treatments, such as radiotherapy and chemotherapy, are affected by irreversible damage to fertility and reproductive performance, resulting in depression, especially in unmarried and childless patients. In addition, ^{131}I treatment should be isolated in a separate closed ward for one week. This lack of social connection which has serious consequences, such as social isolation and interruption of important interpersonal relationships[23]. The present study shows that medical staff should pay more attention to such patients and mobilize social and family members to provide them with psychological support and emotional comfort. In addition, compared with patients without underlying diseases, patients with underlying diseases

tend to have higher levels of depression. First, patients with underlying diseases have higher medical costs than those without such conditions, and consequently exhibit a greater economic and psychological burden. Second, patients with underlying diseases often have severe physical pain and functional impairment, which can cause more severe depression than patients without such conditions[24]. In particular, this phenomenon is more common in patients with hypertension [25], cardiovascular disease[26], and brain edema[11]. Therefore, medical staff and family members should provide more care and companionship to such patients.

Notably, this was a single-center study with a small sample size and did not analyze the long-term concerns of the patients. The risk factors associated with anxiety in patients after DTC surgery must be further verified in large multicenter studies.

CONCLUSION

The anxiety scores of patients with DTC were higher after ^{131}I treatment. Among them, female sex, no spouse, low education level, low family income, basic underlying diseases, and irregularity in taking medicine were influencing factors of anxiety and depression in these patients. In clinical practice, providing patients with targeted nursing interventions according to the aforementioned factors could decrease the risk of anxiety and depression and eventually improve patient prognosis.

ARTICLE HIGHLIGHTS

Research background

Patients were investigated using the self-rating depression scale (SDS) and self-rating scales (SAS). Patients were grouped according to the presence and degree of anxiety and depression. The influencing factors were analyzed, and the appropriate intervention was suggested.

Research motivation

Patients with differentiated thyroid cancer (DTC) after ^{131}I treatment were more prone to anxiety and depression. Clinically, female patients with no spouse, low education level, and low family income, accompanied by basic diseases, and medication irregularity should receive intervention care, thereby reducing the risk of anxiety and depression and improving their prognosis.

Research objectives

The original mean score of SAS and SDS was 50.06 ± 16.10 and 50.96 ± 16.55, respectively; 48.62% (70/144) and 47.22% (68/144) of the patients experiences anxiety and depression, respectively. Educational level, average monthly family income, and medication compliance influenced anxiety. Sex, marital status, and underlying diseases influenced depression ($P < 0.05$).

Research methods

We analyzed 144 patients with thyroid cancer after surgery who received ^{131}I treatment in our hospital from June 2020 to December 2022. The patients were grouped according to their SDS and SAS scores. Single factor and multivariate analyses were used to determine the factors influencing anxiety and depression in patients with DTC after surgery.

Research results

It is crucial analyze the anxiety status and the related risk factors in patients with DTC after surgery, in order to formulate clinical preventive nursing strategies to improve the prognosis of patients.

Research conclusions

This study discussed the anxiety and depression status of patients with DTC after ^{131}I treatment and analyzed their influencing factors.

Research perspectives

Patients with DTC do not comprehend ^{131}I treatment, which is a type of internal radiotherapy, and they easily experience anxiety, fear, depression, and other negative emotions.

FOOTNOTES

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REVIEW

Role of adjunctive nonpharmacological strategies for treatment of rapid-cycling bipolar disorder

Subho Chakrabarti, Amal J Jolly, Pranshu Singh, Nidhi Yadhav

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Abstract

Rapid-cycling bipolar disorder (RCBD) is a phase of bipolar disorder defined by the presence of ≥ 4 mood episodes in a year. It is a common phenomenon characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is resistant to treatment by conventional pharmacotherapy. The existing literature underlines the scarcity of evidence and the gaps in knowledge about the optimal treatment strategies for RCBD. However, most reviews have considered only pharmacological treatment options for RCBD. Given the treatment-refractory nature of RCBD, nonpharmacological interventions could augment medications but have not been adequately examined. This review carried out an updated and comprehensive search for evidence regarding the role of nonpharmacological therapies as adjuncts to medications in RCBD. We identified 83 reviews and meta-analyses concerning the treatment of RCBD. Additionally, we found 42 reports on adjunctive nonpharmacological treatments in RCBD. Most of the evidence favoured concomitant electroconvulsive therapy as an acute and maintenance treatment. There was preliminary evidence to suggest that chronotherapeutic treatments can provide better outcomes when combined with medications. The research on adjunctive psychotherapy was particularly scarce but suggested that psychoeducation, cognitive behavioural therapy, family interventions, and supportive psychotherapy may be helpful. The overall quality of evidence was poor and suffered from several methodological shortcomings. There is a need for more methodologically sound research in this area, although clinicians can use the existing evidence to select and individualize nonpharmacological treatment options for better management of RCBD. Patient summaries are included to highlight some of the issues

concerning the implementation of adjunctive nonpharmacological treatments.

Key Words: Rapid-cycling bipolar disorder; Bipolar disorder; Adjunctive therapy; Nonpharmacological treatment

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Core tip: Rapid-cycling bipolar disorder (RCBD) is a common and highly disabling phase of bipolar disorder. The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive nonpharmacological interventions could be useful. However, their role has not received much attention. This review carried out a comprehensive search to identify the existing evidence on the subject. We found that electroconvulsive therapy, chronotherapy, and psychotherapy could effectively augment medication treatment of RCBD. However, the evidence is limited and methodologically inadequate. Therefore, clinicians have to rely on general guidelines for the optimal use of the available nonpharmacological options while managing RCBD.

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INTRODUCTION

Clinical features of rapid-cycling bipolar disorder

Rapid-cycling bipolar disorder (RCBD) is a phase in the longitudinal course of BD characterized by increased episode frequency. The Diagnostic and Statistical Manual of Mental Disorders (DSM) delineates rapid cycling as a specifier of the longitudinal course of BD rather than a distinct form of the disorder[1]. DSM-5 defines rapid cycling as a minimum of four episodes in the previous 12 mo that meet the diagnostic and duration criteria for hypomanic, manic, or major depressive episodes. Each episode is demarcated by either partial or full remission for at least 2 mo, or a switch to a new episode of the opposite polarity. A proportion of patients have shorter cycles of days to weeks (ultra-RCBD) and some have episodes lasting less than a day (ultradian-RCBD)[2-6]. However, DSM-5 does not include these categories.

The phenomenon of rapid cycling occurs among a significant proportion of patients with BD. The 12-mo prevalence of RCBD in patients from specialized mood disorder clinics is about 20% (range: 4%–27%)[4,6-9]. The prevalence is higher (range: 27%–56%) when ultrarapid and ultradian rapid cycling are included[6,7,10,11]. The rates are also higher in community settings (30%–40%) because these studies have included a wide spectrum of RCBD[9,12-14]. Reviews have estimated the annual prevalence rate of RCBD to be about 18% (range: 5%–33%) and lifetime rates of about 31% (range: 26%–43%)[9,15-18]. The rates obtained by different meta-analytic studies also vary from 15% to 24% (range: 12%–56%)[5,19-21].

Apart from its frequent occurrence, RCBD is characterized by clinical features that make it a severe and disabling phenomenon. Depressive episodes or symptoms appear to be the characteristic clinical presentation of RCBD[5,10,15,17,22]. Patients with BD who have depressive onsets are more likely to develop rapid cycling and patients with RCBD are more likely to present with depressive onsets. Episodes of depression are more frequent and severe in patients with RCBD. Depressive episodes are harder to treat compared with manic ones. As a result of this greater depressive burden, most reviews have also found a higher rate of suicidality in RCBD[5,16,21,23,24]. The frequent recurrence of treatment-resistant depression contributes to the treatment-refractory profile of RCBD. The distress and disability associated with unremitting depression are the main hurdles in effectively managing RCBD[10,13,14,22,25]. Although RCBD is a transient phenomenon that lasts about 2 years in most patients[2,6,16,22,24], many studies have found rapid cycling to persist in > 50% of patients[6,25-28]. A longer duration of rapid cycling, more frequent episodes, a depression-mania-free interval pattern, continuous cycling, agitated depression, temperamental disturbances, and poor response to treatment are associated with the persistence of RCBD[6,8,17,29,30]. Lastly, the consistent finding in the literature is that RCBD is associated with poorer outcomes in terms of severity, recurrence risk, chronicity, comorbidity, and treatment resistance [17-20,31]. Given all these adverse clinical features, it is not surprising that RCBD is associated with greater global functional impairment, poor socio-occupational outcomes, higher levels of disability, poorer quality of life, and greater family burden[2,6,9,16,24]. Thus, RCBD adds a great deal to the overall burden of BD[18].

Pharmacotherapy of RCBD

Since pharmacotherapy is the principal means of treating BD, the primary focus of research has been on the efficacy of medications in RCBD. Several reviews of the subject exist in the current literature. These include narrative reviews[4,24,27,30,32], systematic reviews[6,16,17,29,31], and meta-analyses[5,18,20,21,33] (Supplementary Material includes a complete list of all the reviews consulted).

The main finding of this research is that RCBD is resistant to treatment by conventional pharmacotherapy for BD[6,20,27,29,30]. RCBD comprises the largest group among patients with treatment-resistant BD[34]. Patients with RCBD have poorer treatment response and outcome compared to patients without rapid cycling[26,27,29,30,35]. Although initial studies suggested that RCBD responds poorly to lithium, it is now clear that rapid cycling is resistant to all mood-stabilizing treatments[6,20,36-38]. Treating depressive episodes in RCBD poses greater problems than treating mania/hypomania. The acute efficacy of medications is usually better than their long-term effects[8,11,18,29,32]. Recommendations regarding effective treatment options vary, but most of the evidence appears to favour second-generation antipsychotics, lithium, valproate, lamotrigine, thyroxine, and even antidepressants[17,18,24,31,39]. There is a considerable consensus that response to monotherapy is often inadequate. Therefore, combinations of mood stabilizers and antipsychotics are the more practical, if not the evidence-based options for treatment[17,40-43]. However, the prevailing concern about medication treatments for RCBD is the lack of research data and guidance on suitable evidence-based options, particularly for long-term treatment[17,18,24,29,31]. Not only is there a lack of randomized controlled trials (RCTs) on the subject, but there are also several methodological lacunae such as small sample sizes, uncertainties about the definition of RCBD, and inadequate study designs[6,11,18,20,44].

Nonpharmacological therapy for RCBD

The shortcomings of pharmacological treatment indicate an unmet need for more effective management options for RCBD. Adjunctive nonpharmacological interventions could fill the existing gap in managing RCBD[18,36,45-47]. Treatments such as electroconvulsive therapy (ECT), chronotherapy, and psychotherapy can potentially augment the inadequate response obtained with medications. However, the role of adjunctive nonpharmacological treatments has not received much attention. A systematic review conducted in 2007 considered the different biological and psychotherapeutic options that could augment the pharmacological treatment of RCBD[45]. It found some evidence for the efficacy of ECT and sleep deprivation for acute and maintenance management of RCBD, especially in treatment-resistant patients. Light therapy was not efficacious and there was no data on recurrent transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and psychotherapeutic treatments. The authors acknowledged that the evidence was based only on case reports and open trials and not RCTs. However, they concluded that adjunctive nonpharmacological treatments could be used to manage RCBD based on clinical experience and their usefulness in BD. They recommended the early institution of adjunctive treatments such as ECT in patients who were severely ill and needed immediate relief. Subsequent reviews of the treatment of RCBD have also noted the potential for concomitant use of nonpharmacological treatments and the lack of controlled trials in this area[17,18,32,46,47].

There are several reasons for examining the role of combined pharmacological and nonpharmacological therapy in RCBD. At present, there is no consensus or guidance on the optimal management of RCBD because pharmacological and nonpharmacological treatments have proved less effective[17,18,25,45]. Apart from the inadequate response to standard pharmacotherapy, many other factors make rapid cycling difficult to treat. These include its high prevalence, greater severity, depressive colouring, comorbidities, poorer outcomes, higher levels of disability, side-effect burden, and inadequate medication adherence[15,17,18,24,36]. Adjunctive nonpharmacological treatments can address some of these issues such as persistent depressive symptoms and risks of harm[45], comorbidities[2,10,40], psychosocial stressors, functional impairment[25,32,48-50], and treatment nonadherence[25,30,45,51,52].

Aims of this review

This review aimed to summarize the existing evidence on the role of nonpharmacological therapies as adjuncts to medications in RCBD. It attempted to expand on the previous review[45] by conducting a more comprehensive and updated search of this area.

LITERATURE REVIEW

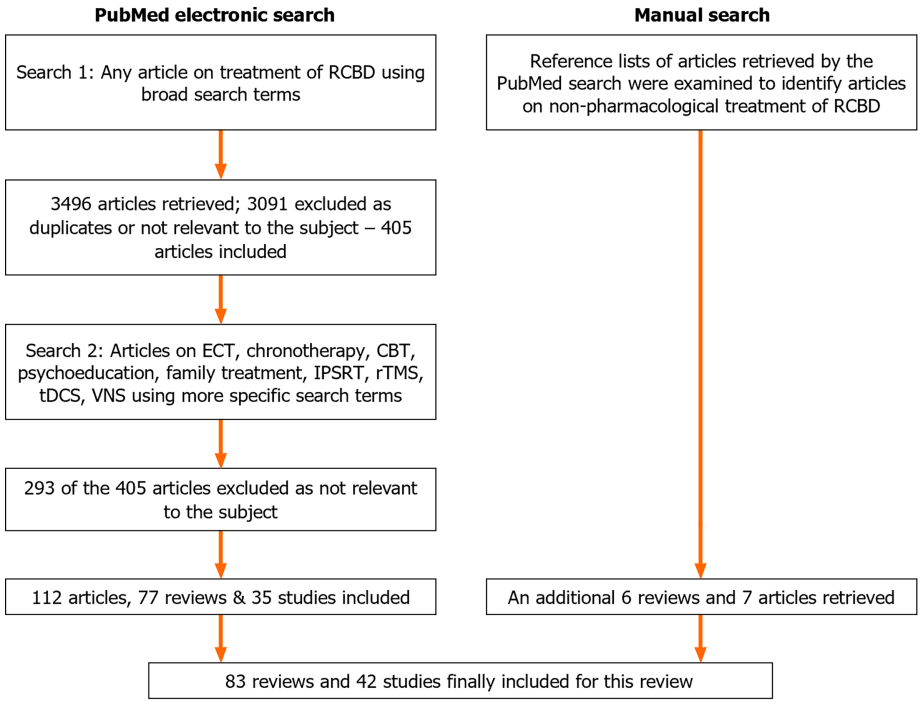
Although this was not a systematic review, it relied on comprehensive electronic (PubMed) and manual searches to identify the existing literature on nonpharmacological treatments in RCBD from 1980 to April 2023. The accompanying figure depicts this search. Supplementary Material includes the details of the search terms used. The Reference Citation Analysis tool was used for searching articles and ranking them according to their impact (Figure 1).

This search identified 53 narrative reviews, 21 systematic reviews, and nine meta-analyses on the treatment of RCBD. These reviews were used to collate information regarding various nonpharmacological therapies in RCBD. A second round of electronic and manual searches identified 17 studies or reports of ECT, 16 of chronotherapy, six of psychotherapy, two of VNS, and one of rTMS. Patients consented to the presentation of their treatment histories. All patient details have been anonymized.

RESULTS

Adjunctive ECT in RCBD

ECT has proven efficacy in BD in treating acute episodes of both mania and depression. It is particularly useful in medication-resistant episodes that are severe, psychotic, or with a high risk of self-harm. The evidence also suggests that maintenance ECT in combination with medication is efficacious for patients with highly recurrent illnesses if they have



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Figure 1 Search strategy for identifying articles on nonpharmacological treatment of rapid cycling bipolar disorder. Search terms are listed in (Supplementary Material). CBT: Cognitive behavioural therapy; IPSRT: Interpersonal and social rhythm therapy; RCBD: Rapid-cycling bipolar disorder; rTMS: Recurrent transcranial magnetic stimulation; tDCS: Transcranial direct current stimulation; VNS: Vagus nerve stimulation; ECT: Electroconvulsive therapy.

responded well to acute ECT[3,45,53-55]. Consequently, ECT has been used for similar indications in patients with RCBD. However, the evidence is limited and based on either case reports or naturalistic studies with small numbers of patients. These studies are included in Table 1[56-72].

Despite these limitations, acute ECT seems to be effective in patients with medication-resistant RCBD with complete or partial remission rates ranging from 70% to 100% in some studies[69,72]. Others have reported lower response rates[64,66,67,70]. Nevertheless, sustained periods of remission and better response to mood stabilizers are reported after acute ECT[64,65,67,70,72]. Acute ECT also reduces the number of episodes and the time spent ill. Though there are fewer studies, the combination of maintenance ECT and mood stabilizers appears to be effective with response rates ranging from 67% to 100%[68,70,71]. Adjunctive maintenance ECT prevents relapses, reduces the need for hospitalization and the length of hospital stay, decreases the time spent in episodes, and increases the duration of interepisodic intervals[68,70,71,73,74]. Patients with RCBD and ultra-RCBD may respond better to ECT than other patients with BD[41,45]. ECT is particularly helpful in patients with RCBD who have failed multiple medication trials, those who are intolerant to medication side effects, and those who are at high risk of self-harm[3,45,49]. ECT is effective in medication-resistant patients with mania[3,30,47,75,76], depression[32,41,68,72,75], or mixed states[49,72] as a part of RCBD. However, the best response is often obtained in patients with bipolar depression[32,41,67,68,72]. Other predictors of good response are depressive episodes with psychotic symptoms or catatonic features[41,68,72]. Minnai *et al*[71] carried out a multivariate analysis to identify the predictors of good response to maintenance ECT in RCBD. Young age, male sex, type II BD, and hyperthymic temperament emerged as factors associated with a higher chance of depression-free intervals with ECT. The better response in those with type II BD and hyperthymic temperament could be because a large proportion of these patients were included in their sample. However, hyperthymic temperament is often associated with antidepressant-induced rapid cycling[6], while ECT may be less likely to cause rapid cycling than antidepressants[4]. The use of ECT has shown to be safe with minimal side effects even when it is combined with mood stabilizers and used for long periods[62,63,68,71,72]. ECT is also less likely than antidepressants to cause manic/hypomanic switches or induce rapid cycling[4,48,49,64,76].

Thus, despite the scarcity of evidence, acute ECT is recommended for treating medication-refractory manic and depressive episodes in RCBD[30,32,45,49,76]. Maintenance ECT can be considered in those patients who improve with acute ECT or relapse on pharmacotherapy[45,73-77]. ECT is more effective if started early in the course of treatment because the outcome is likely to be worse if it is delayed[45,69].

Two of our patients (numbers 1 and 2) received acute ECT with varying degrees of success (Supplementary Material).

Adjunctive ECT in RCBD patient examples

A 72-year-old man with medication-resistant RCBD received two courses of acute ECT in 2017 for episodes of severe depression. The response to the first course was good with complete remission from depression. However, he did not respond as well with the second course a few months later. The depressive episodes did not remit and his rapid cycling continued. He had physical complications during ECT and was unwilling to try ECT further. Later, his rapid cycling

Table 1 Studies of adjunctive electroconvulsive therapy in rapid-cycling bipolar disorder

Ref.	Sample	Results
Case reports		
Berman and Wolpert[56], 1987	18-yr-old woman with medication-resistant RCBD	ECT during mania led to complete remission, which was maintained for 14 mo without medications
Mizukawa *et al* [57], 1991	81-yr-old woman with medication-resistant ultra-RCBD	ECT did not prevent the recurrence of episodes over a period of 35 yr of observation
Benjamin and Zohar[58], 1992	45-yr-old man with treatment-resistant RCBD	Depressive episodes responded transiently to total sleep deprivation and psychotherapy but complete remission was only achieved with acute ECT
Kho[59], 2002	79-yr-old woman with medication-resistant RCBD	ECT and lithium was used successfully during acute and maintenance treatment
Zavorotnyy *et al* [60], 2009	63-yr-old woman with medication-resistant bipolar disorder	The patient developed ultra-rapid cycling during acute ECT, which responded to the continuation of ECT and addition of lithium
Amino *et al*[61], 2011	63-yr-old woman with medication-resistant RCBD	Continuation-ECT for 12 mo prevented rehospitalization
Huber and Burke [62], 2015	67-year-old woman with medication-resistant ultra-RCBD	ECT was used to successfully treat depression and manic episodes that developed on discontinuation of lithium
Kranaster *et al*[63], 2017	21-yr-old woman with medication-resistant ultra-RCBD	ECT was used to successfully treat a treatment-resistant depressive episode
Observational studies		
Kukopulos *et al* [64], 1980	87 patients with RCBD	11 patients treated only with ECT for 7–35 yr remained in remission for long periods
Kukopulos *et al* [65], 1983	87 patients with RCBD	ECT was more effective than antidepressants in treating severe depression and when combined with lithium led to longer remissions
Wehr *et al*[66], 1988	24 patients with medication-resistant RCBD	None of the patients remitted with ECT
Mosolov and Moshchevitin[67], 1990	8 patients with mood stabilizer-resistant RCBD	Acute ECT lead to remission for 6 mo in 3 patients. The number of episodes and the time spent in mood episodes was reduced. Mood stabilizers were more effective following acute ECT treatment
Vanelle *et al*[68], 1994	Four patients with medication-resistant RCBD	Maintenance ECT for 18 mo led to full or partial remission in all 4 patients. Time spent in the hospital was reduced. Response was better in depressive episodes with psychotic symptoms
Wolpert *et al*[69], 2013	Six patients with continuous cycling	ECT started early in the course of cycling was effective in reducing recurrences
Koukopoulos *et al* [70], 2003	43 patients of RCBD who received ECT	11 patients remitted with ECT and mood stabilizer combinations and maintained in this state for 2–36 yr. Temporary improvement was noted in the others. Two out of 3 patients on maintenance ECT had good response
Minnai *et al*[71], 2011	14 patients with medication-resistant RCBD treated with maintenance ECT. Comparisons of 2-yr periods before and after ECT	All patients improved. Eight did not relapse over 2 yr and 6 had only one episode annually. Time spent ill was reduced and interepisodic periods were longer. Young males with type II BD and hyperthymic temperament had better outcome
Mosolov *et al*[72], 2021	1-year prospective study of 30 patients with RCBD and ultra RCBD with poor response to mood stabilizer treatment. Comparisons of 1-yr periods before and after acute ECT	40% achieved and maintained remission with ECT and lithium treatment; 30% showed partial response with the combination and 30% did not respond. Duration of mood episodes was significantly reduced with ECT. Mixed depression with/without catatonia had better response to acute ECT

ECT: Electroconvulsive therapy; RCBD: Rapid-cycling bipolar disorder; type II BD: Bipolar disorder type II; Ultra-RCBD: Ultra-rapid-cycling with shorter cycles of days to weeks; Ultradian-RCBD: Ultradian rapid-cycling with episodes lasting less than a day.

responded to repeated administration of partial sleep deprivation during depressive episodes and dark therapy during hypomanic episodes. A 42-year-old woman with medication-resistant, ultra-rapid, and ultradian cycling was administered ECT in 2005 during an episode of psychotic depression with high suicidal risk. She improved but her cycling did not stop. She was administered ECT again in 2015 for a mixed episode with psychosis and suicidal risk. Response to ECT was inadequate on this occasion and she had physical complications during ECT. Since then, her rapid-cycling pattern has shown a better response to intensive psychotherapy combined with medication. The detailed treatment histories of these patients (Supplementary Material) illustrate some of the disadvantages of ECT in RCBD including the variable response, greater acute than maintenance effects, and the higher risk of adverse effects in some patients[32,45,55,75]. Although ECT is used more commonly in RCBD than in the non-rapid-cycling group, it is still underutilized in RCBD because of these concerns[78,79].

Other neurostimulatory treatments in RCBD

There are few reports of rTMS and VNS treatment in RCBD. A case report described a 60-year-old woman with medication-resistant RCBD who improved after acute administration of rTMS and remained in remission for 6 mo with maintenance rTMS[80]. Another report of a 60-year-old woman with RCBD found that 12 mo of treatment with VNS reduced the severity of her depressive symptoms and the duration of her depressive episodes[81]. Finally, nine patients with treatment-resistant RCBD were treated with VNS for 1 year in a pilot study[82]. They had significant improvements in overall illness severity, the severity of depressive symptoms, and functioning. The VNS treatment was well-tolerated.

Adjunctive chronotherapy in RCBD

Chronotherapy refers to treatment based on controlled exposure to environmental stimuli such as light to alter circadian rhythms or manipulation of the sleep–wake cycle to benefit patients with psychiatric disorders[83-87]. Chronotherapy includes bright light therapy (BLT), wake therapy (total or partial sleep deprivation in the second half of the night), phase-advance of the sleep–wake cycle, triple chronotherapy (combinations of wake therapy, BLT, and sleep phase-advance) dark therapy, blue-light-blocking sunglasses, interpersonal and social rhythm therapy (IPSRT), cognitive behavioural therapy (CBT) for insomnia, and exogenously administered melatonin[84,86,88,89]. These treatments are effective among patients with BD.

Among the various options, BLT appears to be the one best supported by the evidence[86,89]. Several meta-analyses have shown medium to large effects of BLT during acute treatment of bipolar depression[89-93]. It is effective in seasonal and nonseasonal depression[94-98]. Adding BLT to antidepressants or sleep deprivation treatment yields a better response[90,99]. BLT is well tolerated and the risk of manic switches is not increased with it[93,100-103]. However, the efficacy of BLT is based on few RCTs and some meta-analyses have found no conclusive evidence for its efficacy[100,102,103].

The evidence for total or partial sleep deprivation is less convincing. Although 50%–60% of patients respond to a single session of wake therapy, the positive effects of wake therapy are usually transient[86,89,104,105]. The evidence base consists mainly of uncontrolled trials. Moreover, there may be a higher risk of manic switches. Nevertheless, several meta-analyses have concluded that wake therapy combined with medications causes significant reductions in symptoms of bipolar depression[106-109]. Combining sleep deprivation with antidepressants or mood stabilizers, BLT, or sleep phase-advance treatment also sustains its effects[107,110-112]. The treatment might be particularly effective for those with bipolar rather than unipolar depression[113-117]. There is no difference in efficacy between total and partial sleep deprivation[106,108,118,119]. Lastly, the rates of manic switches are low, except in patients with RCBD[104,107,112].

Triple chronotherapy is a treatment regimen designed to prevent the early relapse of symptoms with wake therapy [110,112,116]. It consists of one or more nights of wake therapy, followed by morning administration of BLT, and 3–5 d of sleep phase advance[84]. A systematic review[87] and a meta-analysis[120] showed that triple chronotherapy was effective in bipolar depression. Response rates ranged from 33% to 62% and the effects lasted several weeks. It was not associated with adverse effects and the rates of switching were low.

Dark therapy involves keeping patients with mania/hypomania in dark rooms for extended periods of rest and sleep [84]. This treatment can reduce manic symptoms but has not been examined in RCTs[84,86,117]. A more practical option is the use of glasses that block blue light. This treatment reduced manic and depressive symptoms and improved sleep efficiency in two RCTs[121,122].

A few RCTs of IPSRT have shown positive effects on bipolar depression during acute and maintenance treatment and a single RCT showed that CBT for insomnia improves sleep and decreases depressive symptoms[86,89].

RCBD is the prototypical example of the link between mood disorders and abnormalities of the circadian system and the sleep–wake cycle[28,123-126]. Compared to patients without rapid cycling, the circadian rhythm system in patients with RCBD is more vulnerable to the effects of environmental stimuli, for example, light and dark, irregular sleep patterns and sleep loss, and changes in the social environment such as stressful life circumstances[3,54,55,124,125]. Disturbances in circadian rhythms[3,28,124,126] and social rhythms[28,45,55,127], abnormalities of circadian genes[46,85,128,129], evening chronotypes[125,130], and hormonal abnormalities occur at a higher rate in RCBD[46,85]. However, despite this knowledge and the evidence for the efficacy of chronotherapy in BD, chronotherapy of RCBD is still an evolving area[86]. Since most of the RCTs of chronotherapy in BD usually exclude patients with RCBD, the current evidence is limited to case reports and observational studies with small sample sizes. Table 2 includes these studies and reports of chronotherapy of RCBD[58,70,127,131-143].

Despite the limited evidence, treatments such as wake therapy, BLT, dark therapy, and triple chronotherapy have been used successfully in the acute and maintenance treatment of patients with RCBD. Chronotherapy combined with medications is effective even in patients resistant to medications, ECT, or psychotherapy. There is some concern about the adverse effects of these treatments, particularly the risk of manic/hypomanic switches and exacerbation of rapid cycling with wake therapy. Early studies reported higher rates of switching with wake therapy in RCBD[110,113,114,118,119]. However, these studies mostly used total sleep deprivation. Recent studies of partial sleep deprivation have reported lower rates[115]. Moreover, the high rates are based on a small number of patients with RCBD and the rate of treatment-induced switches is probably no different from the rate of spontaneous switches in RCBD[86,115]. Lastly, such switches can be easily treated or prevented by combining sleep deprivation with medications, BLT, and phase-advance treatment [110,112,115].

Adjunctive chronotherapy in RCBD: patient examples

Four of our patients have been treated successfully with adjunctive chronotherapy. Triple chronotherapy, dark therapy, and blue-light-blocking glasses were used successfully in two inpatients: (1) A 69-year-old woman with a long history of ultra-rapid RCBD was hospitalized after 6 years of unsuccessful treatment with different combinations of medication.

Table 2 Studies of adjunctive chronotherapy in rapid-cycling bipolar disorder

Ref.	Sample	Results
Case reports		
Christodoulou *et al* [131], 1978	26-yr-old woman with rapid-cycling episodes of severe recurrent depression resistant to medications	Inpatient and outpatient total sleep deprivation every week for 36 wk led to remission for a period of 10 mo. The patient committed suicide after stopping the maintenance sleep deprivation treatments
Lovett Doust and Christie[132], 1980	48-yr-old woman with medication-resistant RCBD	Five nights of total sleep deprivation combined with medications during depressive episodes for 8 mo led to reduction in intensity and duration of depression. Switches into hypomania were recorded
Churchill and Dilsaver[133], 1990	47-yr-old woman with rapid-cycling episodes of severe recurrent depression	Partial sleep deprivation on alternate nights combined with an antidepressant led to complete remission from depression for 6 wk
Benjamin and Zohar[58], 1992	45-yr-old man with treatment-resistant RCBD resistant to antidepressants	One night of sleep deprivation was successful in aborting depressive episodes, but led to prolonged hypomania on one occasion and did not prevent the rapid-cycling pattern
Gann *et al*[134], 1993	64-yr-old man with ultradian-RCBD	Total sleep deprivation for 3 nights led to reduction of depressive symptoms for 2 wk. Further improvement occurred with carbamazepine
Eagles[135], 1994	50-yr-old man with medication-resistant ultradian-RCBD	Daily morning BLT for 2 mo produced sustained remission without hypomanic switches
Kusumi *et al*[136], 1995	2 patients with medication-resistant RCBD and nonseasonal depressions	Morning BLT led to improvement in sleep and mood. Withdrawal of BLT did not result in relapse. Remission was maintained for several months
Wehr *et al*[137], 1998	51-yr-old man with medication-resistant RCBD treated with 10–14 h of darkness, rest, and sleep over 1.5 yr	Dark therapy helped in stabilizing sleep, reducing hypomanic symptoms, and attenuating rapid cycling for the period of treatment. Lower doses of antipsychotics were required and hospital stay was shorter
Wirz-Justice *et al* [138], 1999	70-yr-old woman with medication-resistant ultra-RCBD	Rapid-cycling ceased on initiation of 10–14 h of darkness, rest, and sleep. Depression improved with mid-day BLT and remission was achieved with morning BLT. Patient remained on valproate and was stable for a year
Leibenluft and Suppes[127], 1999	42-yr-old woman with medication resistant ultra-RCBD	A lifestyle intervention that ensured a regular sleep–wake schedule in combination with medications led to decrease in rapid cycling
Observational studies		
Papadimitriou *et al* [139], 1981	5 patients with treatment-resistant RCBD	Weekly regimens of total sleep deprivation administered over several months reduced relapses and increased the duration of remissions
Wehr *et al*[140], 1982	9 patients with RCBD treated with 1 night of total sleep deprivation during depressive episodes	Depressive symptoms improved in 8 patients with sleep deprivation but 7 developed mania or hypomania
Papadimitriou *et al* [141], 1993	5 medication-free patients with RCBD treated with total sleep deprivation twice a week for 4 wk	All 5 patients responded to sleep deprivation treatment with > 50% improvement in depressive symptoms and remained in remission for a year with weekly sleep deprivation treatments. Rapid-cycling, young age, female sex, family history of mood disorder and illness duration < 10 yr predicted response. Hypomania was observed in 1 patient
Gill *et al*[142], 1993	3 patients with treatment-resistant RCBD treated with total sleep deprivation and mood stabilizers and antidepressants	Duration of response was significantly better when sleep deprivation treatment was administered late rather than early in the depressive episodes
Leibenluft *et al* [143], 1995	9 patients with RCBD treated with 3 mo of BLT and medications versus 3 mo of only medication treatment	Mid-day BLT was more effective in reducing depressive symptoms and days spent depressed than morning or evening BLT. Morning BLT precipitated hypomanic switches
Koukopoulos *et al* [70], 2003	2 women with RCBD	Sleep deprivation resulted in a temporary improvement of depression

BLT: Bright light therapy; RCBD: Rapid-cycling bipolar disorder; Ultra-RCBD: Ultra-rapid-cycling with shorter cycles of days to weeks; Ultradian-RCBD: Ultradian rapid-cycling with episodes lasting less than a day; Partial sleep deprivation: Sleep deprivation during the second half of the night; Total sleep deprivation: Sleep deprivation for 36 h.

Hypomania at admission responded well to dark therapy within 3–4 d and her antipsychotics could be stopped. She was started on triple chronotherapy when her depressive symptoms began to reappear 2 wk later. With two courses of this treatment, she remitted completely and remained symptom-free for 1 mo. Blue-light-blocking glasses also helped. Unfortunately, chronotherapy was not continued at home. Her rapid cycling resumed and 1 year later she dropped out of treatment; and (2) A 62-year-old woman with medication-resistant RCBD responded partially to morning bright light treatment combined with medication. Her depressive symptoms became less intense and the depressive episodes shorter. However, she was not able to carry out sleep deprivation treatment at home and her ultra-rapid cycling continued. She was hospitalized recently. Her depression responded to two cycles of triple chronotherapy and subsequent hypomanic symptoms responded to dark therapy and wearing blue-light-blocking glasses. She has achieved complete remission with

adjunctive chronotherapy after several years. Triple chronotherapy on an outpatient basis was planned for two more patients with treatment-resistant RCBD. It could not be implemented, but these patients responded to BLT, wake and dark therapy: (1) A 72-year-old man was able to undertake partial sleep deprivation for depression and dark therapy for hypomania at home with the help of his wife. He has achieved almost complete remission for the last 4 years with chronotherapy combined with medication, even though he had responded poorly to medications and ECT earlier; and (2) A 52-year-old woman with ultra-rapid RCBD could not undertake sleep deprivation at home. She has been undergoing morning bright light treatment for depression. Her response has been better since this treatment was added to her mood-stabilizer regimen. She has achieved almost complete remission after a long time. The treatment histories (Supplementary Material) of these patients illustrate the benefits and challenges of administering chronotherapy in RCBD[144]. Although wake therapy, BLT, triple chronotherapy, dark therapy, and blue-light-blocking glasses were successful, conducting these treatments at home was difficult because patients are unwilling to undertake sleep deprivation. Additionally, light boxes are expensive and few patients can afford them.

Adjunctive psychotherapy in RCBD

The existing literature on the treatment of BD indicates that the concomitant use of pharmacotherapy and psychotherapy significantly improves several patient outcomes[145-149]. The most effective forms of psychotherapy are psychoeducational treatments, CBT, and family-focused treatments. These are useful in decreasing symptom severity, reducing the duration of manic and depressive episodes, preventing recurrences, reducing residual depressive symptoms, and decreasing the number and duration of hospitalizations. Additionally, they improve medication adherence, illness management skills, coping abilities, and functional outcomes.

Despite the extensive evidence on the positive effects of adjunctive psychotherapy in BD, there are only a few reports of psychotherapy in RCBD. Table 3 shows these studies[51,58,150-153]. They provide some support for adjunctive psychoeducational treatments, CBT, family intervention, and supportive psychotherapy in RCBD. The outcomes obtained are similar to those shown by RCTs of adjunctive psychotherapy in BD.

The lack of studies on concomitant psychotherapies in RCBD is surprising because these treatments could yield better outcomes in RCBD. Moreover, this is contrary to the advice that psychoeducation, CBT, family interventions, and supportive psychotherapy should be used in RCBD because of the strong evidence base supporting the efficacy of adjunctive psychotherapy in BD[25,32,45,48,51].

Adjunctive psychotherapy in RCBD: patient example

One of our patients with treatment-resistant RCBD received adjunctive supportive therapy. A 42-year-old woman with ultra-rapid and ultradian cycling did not improve with medications and ECT. During the third period of hospitalization in 2015, she was started on regular sessions of structured psychotherapy. The strategies adopted included problem-solving to deal with day-to-day stresses and mood swings and supportive–expressive sessions to deal with more enduring problems such as interpersonal conflicts, and regrets about not working or marrying. She had her best period of mood stabilization for several months while she underwent psychotherapy. Unfortunately, she dropped out of the sessions and was following up irregularly till recently. Nevertheless, she remained free from any severe mood episodes with medications. She has had a recent relapse when medication doses were reduced to minimize side effects but improved with crisis intervention sessions. She has resumed supportive psychotherapy. Her treatment history (Supplementary Material) shows the usefulness of psychotherapy even in those who have not responded adequately to medications or ECT.

DISCUSSION

Treating RCBD remains a challenge for clinicians. Difficulties arise from its high prevalence, severity, poor outcomes, and high disability. The response to pharmacotherapy is often not adequate or complete. Therefore, nonpharmacological treatments are necessary for effectively managing RCBD[18,36,46-48]. However, research on adjunctive nonpharmacological treatments is still scarce[17,18,46,54]. This review shows that there has been limited progress in this area in the last 15 years[45]. A principal reason for the lack of data is the difficulty in conducting methodologically sound treatment trials in RCBD[18,44]. The treatment-resistant nature of RCBD creates further hurdles. Consequently, most RCTs of nonpharmacological treatments for BD usually exclude patients with RCBD.

Nevertheless, there are some promising developments. Not surprisingly, there have been more studies and reports since the 2007 review. Similar to the previous review, the current one also found that most of the evidence favours concomitant ECT as an acute and maintenance treatment in RCBD. Adjunctive acute ECT is effective for severe mood episodes in RCBD that are refractory to medication and have high risk of harm. Adjunctive maintenance ECT may prevent further rapid cycling, especially in those who respond favourably to acute ECT. There is an increasing interest in chronotherapy for BD, but the evidence concerning RCBD is still limited. However, unlike the earlier review, there appears to be preliminary evidence that wake therapy, BLT, dark therapy, and triple chronotherapy can provide better outcomes when combined with medication. Widespread use of these treatments has been hampered by a lack of funding for researchers and lack of awareness and expertise among clinicians[85,154]. Several other factors also hinder the use of chronotherapy, including the cost of equipment such as light boxes, the difficulty of conducting these treatments in outpatient settings or homes, and the problems in ensuring adherence to the treatment protocols[144,155-157]. Lastly, the scarcity of research on adjunctive psychotherapy in RCBD was particularly disappointing. Although psychotherapy appear to be commonly used in clinical settings, the lack of controlled evidence possibly reflects the difficulty in

Table 3 Studies of adjunctive psychotherapy in rapid-cycling bipolar disorder

Ref.	Type of study	Sample	Intervention	Results
Levy and Remick[51], 1986	Observational study	8 women with RCBD	Supportive psychotherapy with patients and family regarding treatment response and adherence	Complete remission in 5 patients and partial remission in 3 patients for 7–40 mo with combined psychotherapy and medications
Spurkland and Vandvik [150], 1989	Case report	13-yr-old girl with RCBD	Family therapy to reduce conflicts and improve adherence	Family therapy combined with medications led to lasting remission
Benjamin and Zohar[58], 1992	Case report	45-yr-old man with treatment-resistant RCBD	Supportive psychotherapy	Psychotherapy provided relief from the rapid-cycling pattern for 3 mo
Satterfield [151], 1999	Case report	33-yr-old man with medication-resistant RCBD	Pharmacotherapy and concomitant CBT	Significant reductions in the severity of manic, depressive, and anxiety symptoms with adjunctive CBT
Reilly-Harrington *et al*[152], 2007	Uncontrolled trial	10 patients with RCBD	CBT included psychoeducation, cognitive restructuring, and teaching illness-management skills	CBT over 5 mo led to significant improvements in depressive symptoms for 2 mo after the treatment in 6 patients who completed the trial
Lenz *et al* [153], 2016	Controlled trial	16 patients with RCBD; 14 wk of adjunctive psychotherapy and 12-mo follow-up	CPT *vs* BT. CPT included psychoeducation and CBT; BT consisted of reading and discussing a book on bipolar disorder	Significant effects of both treatments - reductions in illness severity, reductions in the number of all episodes with CPT and depressive episodes with BT, reductions in the number and duration of hospitalizations, reductions in disability, and improvement in medication adherence and illness concepts. CPT was better than BT

BT: Bibliotherapy; CBT: Cognitive behavioural therapy; CPT: Cognitive psychoeducational therapy; RCBD: Rapid-cycling bipolar disorder.

conducting psychotherapy trials for RCBD. Nevertheless, there is reason to believe that psychotherapy may be effective in RCBD because it can augment the response to medication, reduce acute and residual depression, improve functioning, promote recovery, and decrease family burden[45,48,51,158]. Studies show that childhood maltreatment, stressful life events, and disturbed family environments are more common in RCBD[2,9,25,48,50]. Adjunctive psychotherapy that addresses these factors and reduces psychosocial stress may be helpful in RCBD[45]. Medication nonadherence is a significant problem in BD. It is associated with adverse clinical and psychosocial outcomes among patients and their families. Although some studies show greater nonadherence in RCBD, the majority do not[159]. Nonadherence may be more common in those with more frequent episodes, higher disability, and in those with comorbid substance use disorders[10,40,160,161]. Rapid cycling with these features may contribute to nonadherence and inadequate adherence may worsen cycling[51]. Psychoeducational treatments help improve adherence and attitudes towards medication for BD [145,149]. Similarly, adjunctive psychosocial treatment can positively impact treatment adherence in RCBD by improving treatment attitudes, managing comorbid disorders, and minimizing disability[51,153]. Thus, despite the limited evidence many authors have recommended that adjunctive psychotherapy should form an essential part of the overall management of RCBD[26,32,45,49,158].

CONCLUSION

RCBD is a common phase in the course of BD characterized by greater severity, a predominance of depression, higher levels of disability, and poorer overall outcomes. It is resistant to treatment by conventional pharmacotherapy. The ineffectiveness of conventional pharmacological treatment for RCBD suggests that adjunctive nonpharmacological interventions could be useful but these have not been examined adequately.

According to this review, most of the evidence favoured concomitant ECT as an acute and maintenance treatment for medication-resistant RCBD. Although ECT is effective in refractory mania as a part of RCBD, a better response is obtained in depression with psychotic or catatonic symptoms. ECT is safe and the risk of inducing rapid cycling is low.

Among chronotherapeutic techniques, sleep deprivation or wake therapy has been the option most frequently investigated. Sleep deprivation is effective in relieving depressive symptoms but there is a high rate of relapse and the risk of inducing manic switches. Triple chronotherapy, which combines partial sleep deprivation, bright light treatment, and phase advance of the sleep cycle produces enduring effects and lowers the risk of manic switches. Although there are no studies of triple chronotherapy, examples of patients included in this review suggest that it can be successful in medication-resistant patients. Similarly, there are no studies of dark therapy or blue-light-blocking glasses, but these techniques have been successfully used to treat hypomania in individual patients. Case reports and studies also suggest that bright light treatment can be effective for patients with depression as a part of RCBD.

A few studies provide some support for adjunctive psychoeducational treatments, CBT, family intervention, and supportive therapy in medication-resistant RCBD. The overall quality of evidence for the usefulness of adjunctive nonpharmacological treatment in RCBD was poor and suffered from several methodological shortcomings.

It is apparent from this review that there are large gaps in the existing literature on the usefulness of adjunctive nonpharmacological treatments in RCBD. Therefore, examining the role of these treatments remains a priority for research. However, the current evidence regarding effective pharmacological and nonpharmacological treatment is inconclusive. Thus, clinicians may find treating RCBD a formidable task in the absence of specific guidelines. One option could be to select nonpharmacological treatments effective in BD[27,30,45,49]. Alternatively, treatment decisions can rely on the current evidence on nonpharmacological treatments in RCBD[18]. Clinicians can use this evidence to undertake the sequential or concurrent use of several pharmacological and nonpharmacological interventions[26,45]. Although this remains an exploratory exercise, such combinations are likely to succeed if individualized to meet the needs of patients with RCBD and their families. Table 4 includes principles derived from the existing recommendations that could guide clinicians in managing RCBD. As always, the key to successful treatment of RCBD requires patience, perseverance, and a strong collaborative relationship with patients and their families.

Table 4 Suggestions for the use of adjunctive nonpharmacological treatments in rapid-cycling bipolar disorder

	Suggestions
Goals of acute treatment[18,45]	The priority for acute treatment is to ensure that patients respond to treatment and no longer meet criteria for an acute mood episode
	A rapid response is necessary to provide relief for patients and their families and reduce the risks of self-harm, aggression, and physical complications
	The concurrent and early use of treatments such as ECT or wake therapy for depression, and dark therapy for mania may be considered if there is inadequate response to pharmacotherapy
	Treatments that are likely to be useful during long-term treatment should guide the use of treatments in the acute phases
Goals for long-term treatment[29,30,45,51,55]	Rather than focusing on acute treatment, the primary objective should be to prevent further episodes of rapid cycling
	The model for a chronic medical disorder with acute exacerbations should guide the long-term treatment plan for RCBD
	Adjunctive maintenance ECT, wake therapy, bright light treatment, dark therapy, and triple chronotherapy can be considered at this stage
	Education, support, and the involvement of the family is useful for all patients. Psychoeducational treatments, CBT, family treatment can be implemented if required
Improved functioning rather than complete remission should be the goal of long-term treatment[18,20,25,30]	Full remission and complete absence of recurrences is an unrealistic goal
	Clinicians should focus on an enduring response that consists of reduced frequency, intensity, and duration of mood episodes
	Clinicians should attempt to restore optimal functioning in the occupational, family, and social spheres
Basic tasks[2,4,54,55,162]	Careful diagnosis and comprehensive assessment of the patient including psychosocial factors
	Avoidance of precipitants such as stress, irregular sleep routines, and antidepressant medications when it worsens the course of RCBD
	Treatment of physical and psychiatric comorbidities especially hypothyroidism and substance use
Longitudinal approach and use of life charts [2,26,45,55,163]	Acute episodes should be viewed in the context of the long-term course of bipolar disorder/RCBD
	Life charts may be used to delineate the course of illness, possible precipitants, and treatment response. They might help patients and families understand the course of RCBD and the longitudinal approach to treatment
Use of treatments effective in bipolar disorder[27,30,45,49]	Options for adjunctive nonpharmacological treatment should be chosen based on the evidence for their efficacy in BD
Sequential trials of treatment for long durations[25-27,30,51]	Treatment of RCBD requires several trials of each treatment regimen lasting for about 3–4 mo before the acute-phase efficacy of the treatment regimen can be determined
	Frequent changes in treatment should be avoided since they might worsen rapid cycling
Combining pharmacological and nonpharmacological treatments[25,30,32,45,163]	One option is to add nonpharmacological treatments only in refractory patients in whom several medications have been tried and have failed
	An alternative option recommends the early use of adjunctive nonpharmacological patients even in those patients who are not medication resistant
Monitoring treatment response[17,18,25,35,	More intensive monitoring during acute phases which can be relaxed once the patient becomes more stable

51]	Mood charts can be used to assess response to treatment At least 12 mo of treatment is required to determine the efficacy of long-term treatment
Working with patients and families[4,32,45,51,127]	Education: explaining RCBD, its causes, and the treatment approach including lifestyle changes is necessary for ensuring the collaboration of patients and families. Psychoeducational treatments that reduce stress, improve attitudes to treatment, enhance treatment engagement, and reduce caregiver burden can be tried. CBT is another option Support: ongoing support for patients and families is essential. This can be provided by developing a strong collaborative relationship. Nonadherence can also be addressed by fostering a strong treatment alliance Patience: the protracted nature of the illness requires the clinician to accept that it will take a long time for the results to become apparent. Patience and perseverance on the part of patients and families has to be stressed repeatedly so that they learn to focus on long-term goals Sleep hygiene: regular sleep routines can be advised in all patients. Chronotherapeutic techniques can be tried when required and feasible

CBT: Cognitive behavioural therapy; ECT: Electroconvulsive therapy; RCBD: Rapid-cycling bipolar disorder.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Dexmedetomidine mediates the mechanism of action of ferroptosis in mice with Alzheimer's disease by regulating the mTOR-TFR1 pathway

Li Qiao, Gang Li, Hong-Xun Yuan

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Abstract

BACKGROUND

Alzheimer's disease (AD) is the most common neurodegenerative disorder, and there are currently no effective drugs to delay progression of the disease. Ferroptosis may play a vital part in AD, and is therefore receiving increasing attention by researchers.

AIM

To investigate the effects of dexmedetomidine (Dex) on ferroptosis in AD mouse hippocampus.

METHODS

Hippocampal neurons (HNs) HT22 were induced by amyloid β-protein (Aβ) and both *in vitro* and *in vivo* AD mouse models were prepared *via* injections. The cell-counting kit-8 assay and immunofluorescence technique were adopted to determine cell proliferation activity and intracellular Fe^{2+} levels, and the TBA method and microplate method were employed for malondialdehyde and glutathione measurements, respectively. Hippocampal tissue damage was determined using hematoxylin and eosin and Nissl staining. Mouse learning and memory ability in each group was assessed by the Morris water maze test, and the expression levels of mammalian target of rapamycin (mTOR) signal molecules and ferroptosis-related proteins transferrin receptor 1 (TFR1), SLC7A11 and glutathione peroxidase 4 were examined by western blotting.

RESULTS

Dex enhanced lipid peroxidation and iron influx in mouse HNs in both *in vitro* and *in vivo* experiments, while inhibition of the mTOR axis blocked this process. These findings demonstrate that Dex can inhibit ferroptosis-induced damage in mouse HNs by activating mTOR-TFR1 signaling to regulate ferroptosis-associated

proteins, thus alleviating cognitive dysfunction in AD mice.

CONCLUSION
Dex can activate the mTOR-TFR1 axis to inhibit ferroptosis in mouse HNs, thereby improving the learning and memory ability of mice.

Key Words: Dexmedetomidine; Ferroptosis; Alzheimer's disease; Mammalian target of rapamycin; Mice

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Core Tip: Iron death of nerve cells caused by iron overload is an important factor in various neurodegenerative diseases, including Alzheimer's disease (AD). The classic mammalian target of rapamycin (mTOR) signaling pathway regulates the metabolism of iron ions by regulating transferrin receptor 1 (TFR1), thereby maintaining the intracellular iron balance. It has been shown that dexmedetomidine (Dex) inhibits the release of inflammatory factors and plays a neuroprotective role, thereby improving cognitive dysfunction in elderly rats. The Dex effectively improved hippocampal neuronal loss, cognitive dysfunction, learning and memory abilities in AD mice by regulating the mTOR-TFR1 signaling pathway to reduce iron death.

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INTRODUCTION

With the current escalation in global aging, neurodegenerative disorders (NDDs), including Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease, have attracted growing attention from researchers and have become a research hotspot[1]. Ferroptosis is a non-apoptotic programmed cell death associated with cytotoxicity caused by iron-dependent lipid peroxide accumulation, and iron overload is the key to triggering the occurrence of cell ferroptosis[2]. It is reported that iron deposition in brain tissue increases significantly with age, ultimately affecting nerve cell function[3-5]. Immunohistochemical tests confirmed that neuronal ferroptosis caused by iron overload in the cerebellum, cortex and hippocampus was an important factor leading to NDDs. The mammalian target of rapamycin (mTOR) is a classical autophagy-dependent regulatory protein that affects cell death pathways such as autophagy, apoptosis, and ferroptosis [6]. The classic mTOR axis influences iron ion metabolism by modulating transferrin receptor 1 (TFR1), thus maintaining the intracellular iron balance[7]. In addition, the high intracellular Fe^{2+} level leads to the inhibition of mTOR expression, resulting in intracellular iron homeostasis imbalance and consequently oxidative stress (OS)-induced ferroptosis[8]. Dexmedetomidine (Dex) is a highly selective α2 adrenergic receptor agonist that not only exerts analgesic and sedative effects by inhibiting sympathetic nerve activity, but is also neuroprotective against various brain injuries[9,10]. However, its underlying mechanism is unknown. Several studies have found that, by regulating ferroptosis, Dex can play a protective role in liver injury, myocarditis, cerebral ischemia-reperfusion, and craniocerebral injury[11-13]. In addition, Dex was shown to significantly improve neurocognitive function and effectively inhibit the abnormally high level of OS in NDDs and brain trauma, thus reducing inflammation[14]. Yet, it remains to be confirmed whether and how Dex can be neuroprotective by regulating ferroptosis in AD, a NDD. The experimental results of this study show that Dex can inhibit iron overload by activating the mTOR-TFR1 axis, thus maintaining iron homeostasis, protecting hippocampal neurons (HNs) from ferroptosis, and playing a neuroprotective role in AD mice, which can provide insights into ferroptosis-induced neuronal death.

MATERIALS AND METHODS

Experimental animals

Forty adult male specific pathogen free C57BL/6 mice, aged 8-10 wk and weighing (23 ± 2) g, were raised under constant temperature (25 ± 1 °C), humidity (60% ± 5%), and an alternating light/dark (12/12 h) cycle. The experiments were carried out after 7 d of adaptive feeding with rat chow and water available *ad libitum*. All animal experiments were carried out after obtaining approval from the Experimental Animal Ethics Committee of Peking University International Hospital.

Experimental reagents

Mouse HT22 HNs and dedicated cell culture medium (Procell Life Science & Technology, Wuhan, China); Dex (Chia Tai

Tianqing Pharmaceutical Group, Nanjing, China); BCA analysis kit (Boster, China); cell-counting kit-8 (CCK-8; Dojindo, Japan); Perls stain (Thermo Fisher Scientific; United States); Nissl stain (Jiangsu KeyGEN Biotech, Nanjing, China); polyvinylidene fluoride (PVDF) membrane (Millipore, United States); malondialdehyde (MDA) Colorimetric Assay Kit (Abcam, United States); Mito-FerroOrange (Dojindo Molecular Technologies, Tokyo, Japan); 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) fluorescence probe (Solarbio, Beijing); Lipofectamine 2000 (Invitrogen, United States); siRNA mTOR (Shanghai Sangon Biotech, China); specific primary antibodies (Abs) and HRP labeled anti-p-mTOR, TFR1, SLC7A11 and glutathione peroxidase 4 (GPX4), as well as the internal reference GAPDH secondary Ab (Abcam, United States) were used in this study.

Experimental instruments

The Morris water maze (MWM) system (Noldus, Netherlands); inverted fluorescence biomicroscope (Zeiss, Germany); E0970 Microtome Cryostat (Beyotime Biotech, Beijing, China); enhanced chemiluminescence (ECL) detection system (Bio-Rad, Hercules, CA, United States); Multiskan FC microplate reader (Thermo Scientific, United States); western blot Electrophoresis Instrument and Trans-Blot instrument (Bio-Rad, United States) were used in this study.

Animal grouping and model building

Forty C57BL/6 mice were randomized to the sham, amyloid β-protein (Aβ), Dex, and Dex + rapamycin (RAPA) groups, with 10 mice in each group. After anesthesia by intraperitoneal injection of 10% chloral hydrate (dosage: 0.1 mL/10 g body weight) in all C57BL/6 mice, 5 μL of condensed Aβ (80 pmol/μL) was injected as a single bolus into mouse bilateral ventricles using a micro-sampler, and the needle was left in place for 2 min before bandaging. The sham group was injected with an equal amount of normal saline into the bilateral ventricles. The Dex group was intraperitoneally injected with Dex (dosage: 20 μg/kg) dissolved in 0.9% sterile saline, once a day for 4 consecutive weeks; on this basis, the Dex + RAPA group was additionally injected with 2 mg/kg of RAPA dissolved in 2% dimethylsulfoxide. The sham and Aβ groups were given the same amount of 0.9% sodium chloride solution, and the remaining treatment was the same as above.

MWM test

After the above treatment, the mice underwent the MWM test for 5 d. During the training phase (the first 4 d), the mice were trained once a day at a fixed time, and the time they took to find the platform within 120 s (*i.e.*, escape latency) and the swimming trajectory map were recorded. On the fifth day, the platform was removed for spatial exploration experiments, and the running trajectory, escape latency, number of platform crossings, and target quadrant residence time were recorded.

Animal tissues

The mice were anesthetized with chloral hydrate after the MWM test. The right auricle was then cut open and the left ventricle was perfused with 4% paraformaldehyde solution. After sacrifice on ice by cervical dislocation, the mouse hippocampus tissues on both sides were quickly removed, some of which was stored in liquid nitrogen for later use. The remaining portion was fixed in 4% paraformaldehyde, and after gradient dehydration with ethanol, it was embedded in paraffin and sliced into sections (4 μm). The pathological changes of HNs were observed under a light microscope after conventional hematoxylin-eosin (HE) staining.

Nissl staining

Part of the hippocampus tissue was frozen in liquid nitrogen to prepare frozen sections (5 μm), which were degreased with a gradient concentration of ethanol solution and then washed three times with ddH_2O for 30 s each time. Cresyl violet (Nissl) dye solution (0.1%) was added dropwise and left at 56 °C for 1 h. After dyeing, the slices were washed with ddH_2O for a further three times. Next, color separation was carried out for 2 min with acid alcohol differentiation solution (0.5%), followed by immersion in 100% ethanol for 30 s and xylene permeation for 1 min. After mounting with neutral gum, each slice was observed microscopically (400 ×) with five visual fields randomly selected, and the number of nerve cells was recorded (n = 5).

Prussian blue staining

Paraffin slices were routinely dewaxed and rinsed with distilled water for 1 min. Perls staining solution, which was homogeneously formulated by mixing reagent A1 with reagent A2 in equal amounts, was used immediately after preparation. The sections were washed again with distilled water after 30 min of Perls staining. They were then nucleated with the nuclear fast red stain kit (reagent B) for 10 min and rinsed with distilled water, followed by conventional dehydration, vitrification, neutral-gum mounting, and air drying. The Prussian blue deposition in hippocampal tissue was observed under a light microscope. Five visual fields in each slice were randomly photographed, and the percentage of Prussian blue staining (PBS) positive area in the whole area was measured by image analysis.

Cell cultivation and treatment

Mouse HT22 HNs were immersed in HT22 dedicated culture medium and cultivated in a 37 °C, 5% CO_2 and 95% humidified cell incubator, and the well-grown cells were selected for the following experiment. All neuron cell lines used were within 20 passages. Grouping: (1) Blank control group: HT22 cells was cultured with HT22-dedicated medium without any other treatment; (2) Aβ model group: HT22 cells were treated with Aβ at a final concentration of 20 μmol/L and cultured for 24 h; (3) Dex group: Following 2 h of treatment with Dex at a final concentration of 5 μmol/L, HT22 cells

were cultured with Aβ at a final concentration of 20 μmol/L for 24 h; and (4) Dex + mTOR siRNA (si-mTOR) group: After transfection with si-mTOR using Lipofectamine 2000, HT22 cells were treated with 5 μmol/L Dex for 2 h and then cultured with 20 μmol/L Aβ for 24 h.

CCK-8 assay

HT22 cells (1×10^5/mL) were seeded with 100 μL of cell suspension per well on a 96-well culture plate and cultured for 24 h. After different treatments, the CCK-8 reagent was added at 10 μL/well for 1 h at 37 °C, after which the absorbance value at 450 nm was measured by a microplate reader to assess cell viability.

Intracellular Fe^{2+} level detection

Intracellular Fe^{2+} levels were measured with Mito-FerroOrange. After different cell treatments, the supernatant was discarded. Following three rinses with HBSS, 2 mL of cells were added to every 2 μL of Mito-FerroOrange working solution and incubated at 37 °C for 30 min. The cells were observed by confocal fluorescence microscopy and the fluorescence intensity level was determined.

OS determination

Cell lipid peroxidation (LPO) was detected by BODIPY-C11 labeled fluorescent staining. 5 μM BODIPY-C11 was added to the cells and incubated in the dark for 20-30 min. After staining, the cells were collected by centrifugation and the LPO level was calculated by measuring the fluorescence intensity. In addition, HT22 cells were stained with 10 μM DCFH-DA fluorescent dye for 30 min, and were then collected for fluorescence intensity measurement, which reflected the reactive oxygen species (ROS) level. According to the manufacturer's instructions, the level of MDA, the final product of LPO, was determined using the MDA colorimetric assay kit. The absorbance of reactants was calculated and determined according to the standard curve to evaluate the MDA concentration.

Western blot

Following the standard protocol, HT22 cells in each group were lysed in RIPA buffer to extract the protein supernatant. In addition, the protein supernatants were isolated from the hippocampus following cryopreservation with liquid nitrogen and homogenized. The protein concentration was then quantitatively detected with a BCA assay kit. Following dilution and boiling, the protein samples were separated by 6%-10% polyacrylamide gel electrophoresis, after which semi-dry electroblotting was performed to transfer the protein bands to a PVDF membrane. The membrane was blocked in 5% defatted milk for 1 h, incubated with specific primary Abs at 4 °C overnight, washed with TBST twice, and incubated with HRP-labeled anti-p-mTOR, TFR1, SLC7A11 and GPX4 as well as the GAPDH specific secondary Ab (internal reference) for 1 h at ambient temperature. After dropwise addition of the ECL substrate to the protein bands, the grayscale values of the target protein bands were measured using the ECL detection system and the relative expression was calculated by the ratio of the grayscale values of the target protein to the reference protein.

Statistical analysis

Statistical processing and mapping of the data were performed using GraphPad Prism 7.0. Continuous variables that conformed to a normal distribution were described as the mean ± standard deviation (mean ± SD); statistical inter-group and multi-group differences, indicated by $P < 0.05$, were identified using the *t*-test and one-way variance analysis, respectively.

RESULTS

Dex blocks Aβ-induced cytotoxicity of mouse HNs by activating mTOR

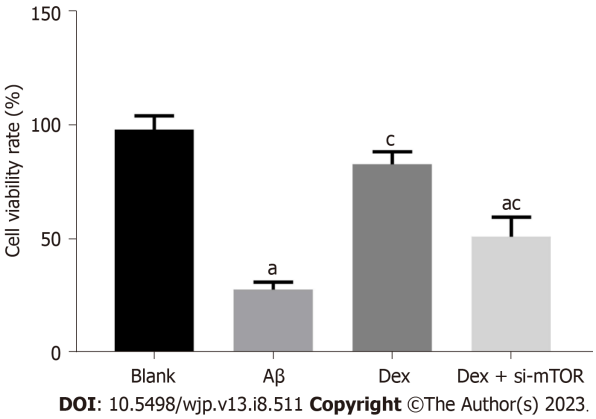
In order to confirm whether Dex can alleviate the cytotoxicity of mouse HNs, we first measured the impact of Dex on the viability of Aβ-treated mouse HNs. As shown by the CCK-8 assay (Figure 1), Aβ-treated HNs showed notably weakened cell viability compared with HNs from blank control mice ($P < 0.05$), while Dex treatment significantly restored the viability of Aβ-treated HNs ($P < 0.05$); in addition, the viability of Dex + si-mTOR treated cells was significantly lower than that of Dex-treated cells ($P < 0.05$). These findings suggest that Dex can alleviate the cytotoxicity of Aβ-treated mouse HNs, while inhibiting mTOR can block the effect of Dex treatment on cytotoxicity.

Dex inhibits the increase of Fe^{2+} level in Aβ-treated mouse HNs by activating mTOR

To further examine whether ferroptosis was responsible for Aβ-induced inhibition of cell proliferation, we first measured the impact of Dex on Fe^{2+} levels in Aβ-treated mouse HNs. As shown in Figure 2, Aβ-treated mouse HNs showed markedly elevated Fe^{2+} levels ($P < 0.05$), which were significantly reduced by Dex treatment ($P < 0.05$); moreover, Dex and si-mTOR co-treatment led to statistically higher Fe^{2+} levels in Aβ-treated HNs compared with Dex treatment alone ($P < 0.05$). These results show that Dex can inhibit the Aβ-induced increase of Fe^{2+} level in mouse HNs, and this inhibition is achieved by activating mTOR.

Dex reduces Aβ-induced OS in mouse HNs by activating mTOR

The increase of intracellular OS level in mouse HNs is also an important feature of ferroptosis. Significantly elevated ROS, LPO and MDA levels were observed in Aβ-treated mouse HNs ($P < 0.05$), which were reduced after Dex treatment ($P <$



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Figure 1 Comparison of the activity levels of hippocampal neurons in mice in the different treatment groups. $^{a}P < 0.05$, compared with the blank group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA.

0.05); in addition, Dex and si-mTOR co-treated cells showed higher ROS, LPO and MDA levels than those treated with Dex alone ($P < 0.05$), as shown in Figure 3. These results suggest that Dex treatment can alleviate the increase in intracellular OS level induced by Aβ in mouse HNs, and inhibiting mTOR can block this process.

Dex blocks Aβ-induced ferroptosis in mouse HNs through regulation of the mTOR-TFR1 axis

In order to confirm whether the antioxidant protection and iron metabolism effects of Dex are related to ferroptosis in mouse HNs, we performed western blot to determine the expression levels of the mTOR signal molecular protein p-mTOR and ferroptosis-associated marker proteins TFR1, SLC7A11, and GPX4 in Aβ-treated mouse HNs. The results showed a marked reduction in p-mTOR, SLC7A11, and GPX4 protein expression in mouse HNs induced by Aβ, and an obvious increase in TFR1 protein expression ($P < 0.05$). Compared with the Aβ group, Dex-treated cells showed enhanced p-mTOR, SLC7A11 and GPX4 levels, and decreased TFR1 ($P < 0.05$). Simultaneous treatment with Dex and si-mTOR further reduced p-mTOR, SLC7A11 and GPX4 protein levels, and promoted TFR1 protein expression, and these changes were statistically significant ($P < 0.05$), as shown in Figure 4. Therefore, Dex can significantly activate mTOR signaling and reduce Aβ-induced ferroptosis in mouse HNs by modulating the mTOR-TFR1 axis.

Dex alleviates hippocampal tissue damage in AD mice by activating mTOR

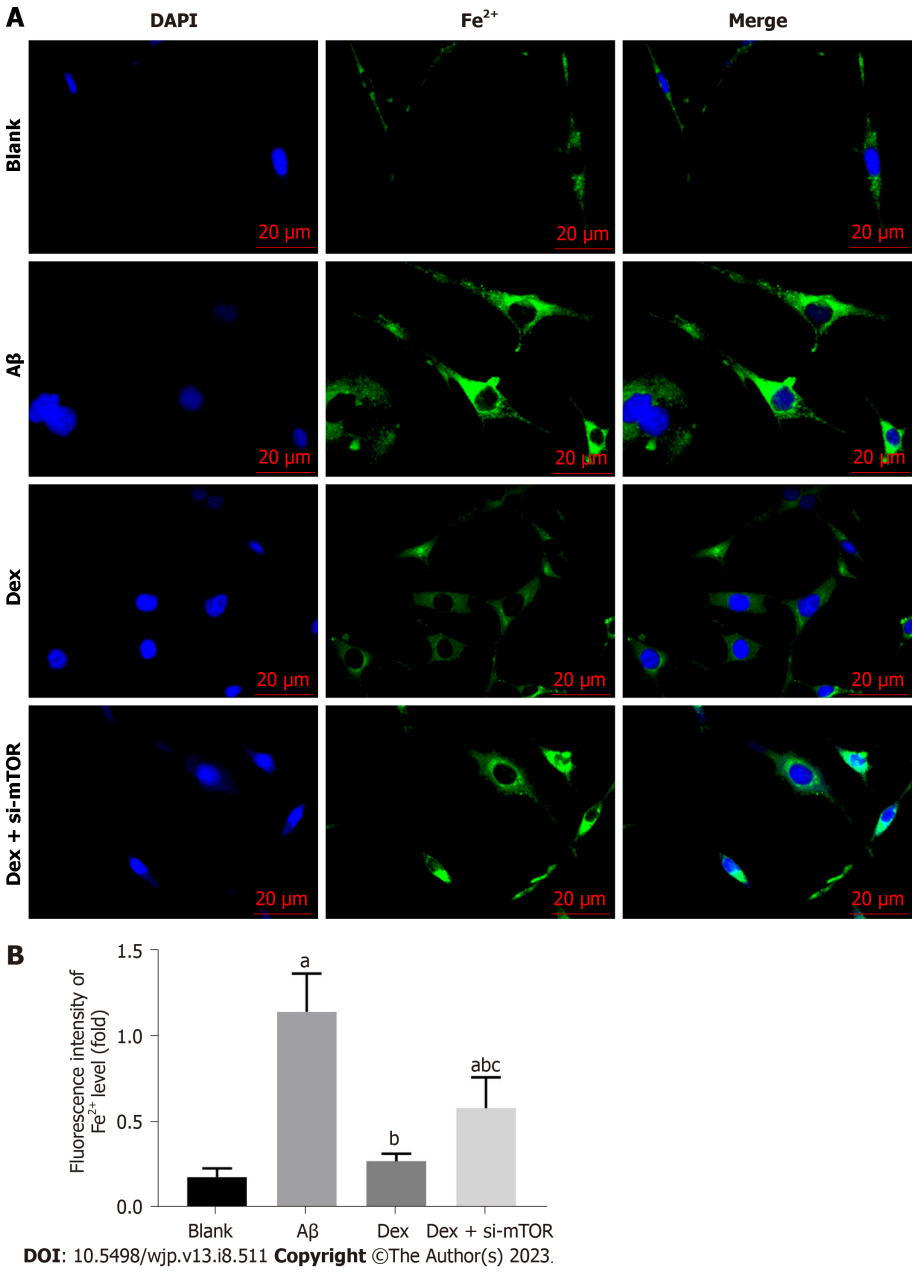
According to HE staining results, the HNs in Sham mice were evenly distributed, with abundant cytoplasm, clear nuclei, and normal and intact cell morphology and structure; in the Aβ group, the HNs were sparsely arranged and disordered, with less cytoplasm, unclear cell morphology and atrophy; the HNs in the Dex group showed less neuronal atrophy, with uniform cell distribution, regular arrangement, and deep cytoplasmic staining; while HNs in the Dex + RAPA (mTOR inhibitor) group showed more atrophy, more irregular arrangement and less clear cell morphology than the Dex group. Nissl staining results demonstrated that Nissl bodies in the hippocampus of the sham group were closely arranged and in large numbers; a notably reduced number of Nissl bodies was observed in the hippocampus of the Aβ model group; following Dex treatment, the number of Nissl bodies in the hippocampus of the Aβ model mice increased significantly; while the Nissl body count in the hippocampus of the Dex + RAPA group decreased markedly compared with the Dex group (Figure 5). These findings indicate that Dex can mitigate Aβ-induced hippocampal tissue damage and increase the number of HNs in AD mice, and this process is realized through activation of mTOR signaling.

Dex mitigates OS and Fe^{2+} levels in AD mouse hippocampus by activating mTOR

To confirm whether the antioxidant protection of Dex is related to its regulation of iron metabolism, we further evaluated the influence of Dex treatment on OS and Fe^{2+} level in the mouse hippocampus. MDA in the hippocampus of AD model mice induced by Aβ was significantly increased compared with Sham mice, while glutathione (GSH) was markedly reduced ($P < 0.05$). The Dex group showed reduced MDA and elevated GSH compared with the Aβ group ($P < 0.05$); moreover, co-treatment with Dex and RAPA in AD mice showed enhanced MDA and decreased GSH in the hippocampus compared with Dex-treated AD mice ($P < 0.05$). In addition, based on PBS results, the level of Fe^{2+} in hippocampal tissue of Aβ-treated AD model mice was significantly increased ($P < 0.05$), and was markedly reduced after Dex treatment ($P < 0.05$); moreover, the Dex + RAPA group showed higher Fe^{2+} in hippocampal tissue than that in the Dex group ($P < 0.05$) (Figure 6). Thus, Dex can markedly alleviate iron deposition and OS in Aβ-treated AD mouse hippocampus by activating mTOR.

Dex reduces cognitive dysfunction in AD mice by activating mTOR

The MWM test was used to evaluate the learning and memory ability of mice in each group. AD mice in the Aβ group showed markedly prolonged escape latency, and a statistically significant reduced number of platform crossings and target quadrant residence time ($P < 0.05$). The escape latency, number of platform crossings and target quadrant residence time of AD mice in the Dex group and Dex + RAPA group were significantly improved compared with the Aβ group ($P < 0.05$), with improvement in cognitive dysfunction in the Dex group as compared with the Dex + RAPA group ($P < 0.05$),



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Figure 2 Comparison of the level of Fe^{2+} in mouse hippocampal neurons in the different treatment groups. A: Green fluorescence represents intracellular iron levels, and quenching of calcein fluorescence reflects iron uptake by chondrocytes. Scale bar: 20 μm; B: Fluorescence intensity. $^{a}P < 0.05$, compared with the blank group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; DAPI: 4',6-diamidino-2-phenylindole.

as shown in Table 1. These results suggest that Dex treatment improves the learning and memory ability of Aβ-treated AD mice, while RAPA exerts negative effects on this improvement.

Dex reduces ferroptosis in AD mice by modulating mTOR-TFR1

From the western blot analysis (Figure 7), it was found that the Aβ group had markedly reduced mTOR, SLC7A11 and GPX4 protein levels and elevated TFR1 protein expression in the hippocampus compared with the sham group ($P < 0.05$); Dex treatment enhanced mTOR, SLC7A11 and GPX4 protein expression in AD mice, and decreased TFR1 protein expression ($P < 0.05$); furthermore, the injection of RAPA effectively blocked the regulation of Dex on the expression of mTOR signaling molecules and ferroptosis markers TFR1, SLC7A11 and GPX4 in AD mouse hippocampus ($P < 0.05$). Therefore, Dex can mitigate ferroptosis in AD mouse hippocampus by activating the mTOR-TFR1 axis.

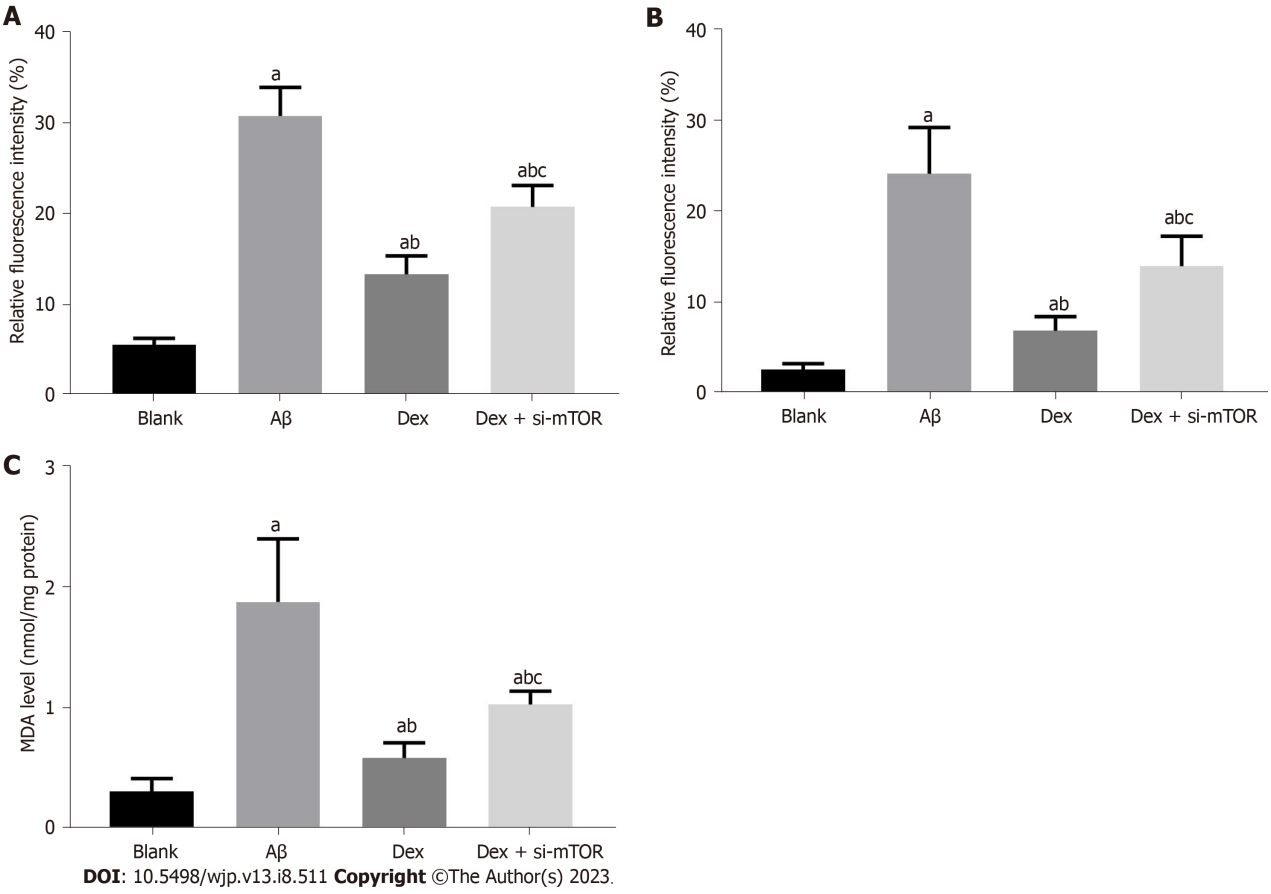
DISCUSSION

AD is the most common progressive NDD, and is mainly caused by synaptic loss of neurons in the cerebral cortex and

Table 1 Comparison of escape latency, number of platform crossings and target quadrant residence time in the different treatment groups

Groups	Sham (*n* = 10)	Aβ (*n* = 10)	Dex (*n* = 10)	Dex + rapamycin (*n* = 10)
Escape latency (s)	5.38 ± 0.53	42.20 ± 3.89[a]	13.81 ± 1.64[a,b]	22.75 ± 3.06[a,b,c]
Number of platform crossings (times)	7.26 ± 0.82	1.38 ± 0.35[a]	5.90 ± 0.61[a,b]	3.24 ± 0.43[a,b,c]
Target quadrant residence time (s)	38.46 ± 5.27	7.92 ± 1.69[a]	30.40 ± 4.26[a,b]	22.52 ± 2.78[a,b,c]

[a]$P < 0.05$, compared with the sham group.
[b]$P < 0.05$, compared with the amyloid β group.
[c]$P < 0.05$, compared with the dexmedetomidine group.
β: Amyloid β; Dex: Dexmedetomidine.



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Figure 3 Comparison of oxidative stress index levels in mouse hippocampal neurons in the different treatment groups. A and B: Hippocampal neurons were stained with DCFH-DA or C11 BODIPY fluorescent probe, reactive oxygen species (A) and lipid peroxidation levels (B) were calculated by measuring fluorescence intensity; C: Absorbance of the oxidation reaction was measured to evaluate the cellular malondialdehyde level using kits. [a]$P < 0.05$, compared with the blank group; [b]$P < 0.05$, compared with the amyloid β group; [c]$P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; MDA: Malondialdehyde.

hippocampus, and the death of brain neurons[15]. In recent years, ferroptosis has been found[16-18] to be the underlying mechanism of neuron loss in many NDDs, and the "ferroptosis hypothesis" has been proposed for AD. GPX4 mRNA and protein levels are reported to be aberrantly down-regulated in the brains of patients and mice with AD[19,20]. GPX4 relies on reduced GSH to catalyze LPO reduction, which is considered the key regulator of ferroptosis, while the inhibition of GPX4 can lead to LPO accumulation, a hallmark feature of ferroptosis that is considered an early event in the pathological process of AD[21]. During the process of iron imbalance, free Fe^{2+} released by ferritin degradation reacts with lipids through the Fenton reaction, and eventually forms lipid peroxy radicals and hydroperoxides, leading to LPO accumulation, the prime reason for ferroptosis[22]. The present study demonstrated that there were significant iron deposits and increased ROS and lipid oxidation levels in Aβ-treated mouse HNs and AD mouse hippocampus tissues, and Aβ treatment promoted the expression of iron transfer-related protein TFR1 and decreased the expression levels of ferroptosis regulation associated proteins GPX4 and SLC7A11. Furthermore, *in vitro* and *in vitro* studies demonstrated the

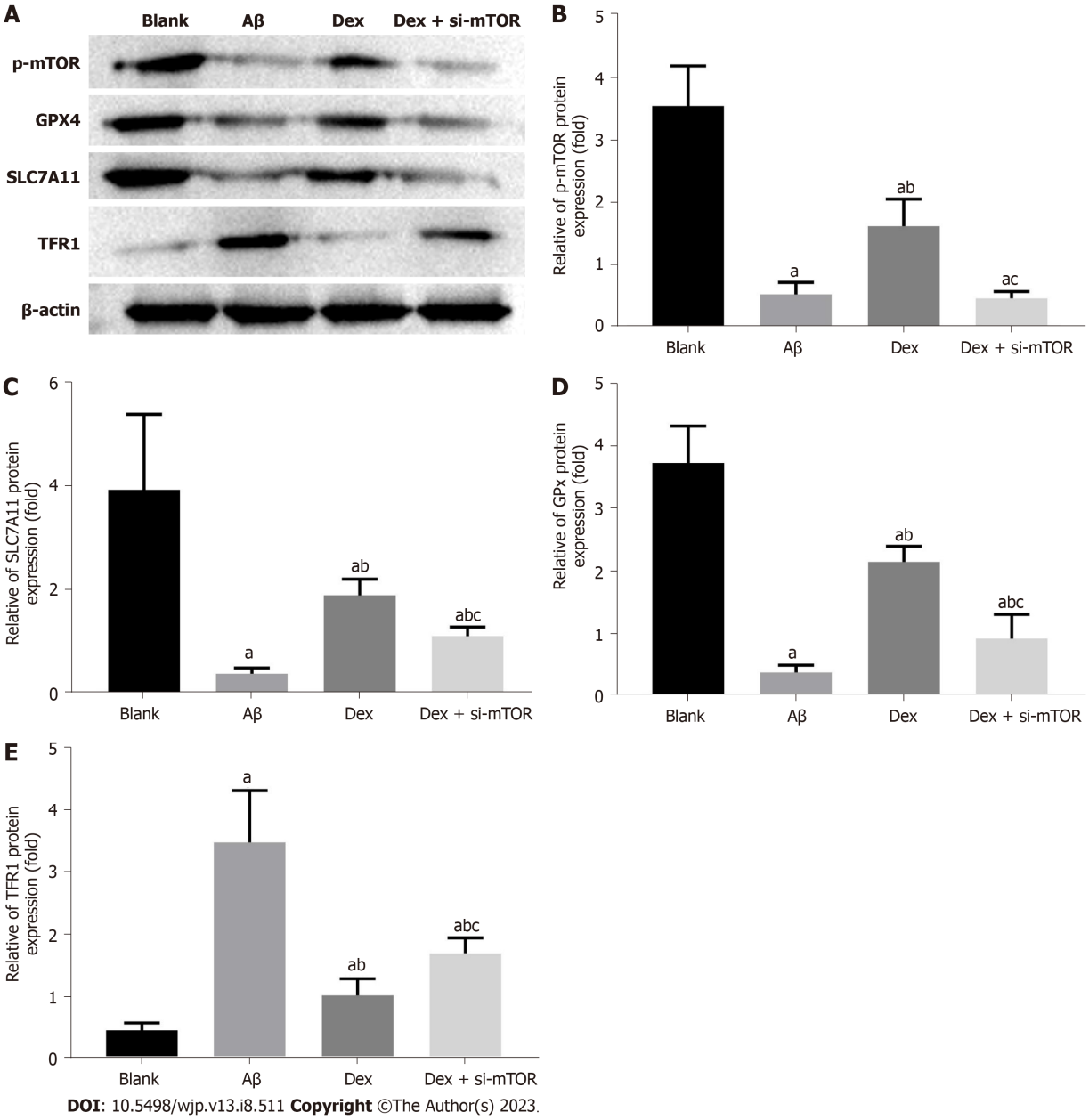


Figure 4 Comparison of iron death-related protein levels in hippocampal neurons of mice in the different treatment groups. A: Expression levels of p-mammalian target of rapamycin, SLC7A11, glutathione peroxidase 4, and transferrin receptor 1 were detected by western blot; B-E: The relevant data. [a]*P* < 0.05, compared with the blank group; [b]*P* < 0.05, compared with the amyloid β group; [c]*P* < 0.05, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; GPX4: Glutathione peroxidase 4; TFR1: Transferrin receptor 1.

occurrence of ferroptosis during AD. Thus, the above research suggests the important role of ferroptosis in AD.

Moreover, in the *in vivo* and *in vitro* experiments, it was found that Dex effectively reduced ferroptosis in HNs of AD mice. Previous studies have confirmed the neuroprotective effects of Dex, as it can inhibit the neuroinflammatory reaction and reduce OS, and has an anti-inflammatory and antioxidant role[23]. It has also been shown to prevent early cognitive dysfunction in senile mice after surgery[24]. Sun *et al*[25] also reported that Dex reduced Aβ1-induced HN apoptosis and OS responses in mice by modulation of the miR-129/YAP1/JAG1 axis, thus alleviating cognitive impairment and improving cognitive function in AD mice. In the present study, the number of Nissl bodies in the hippocampus of Aβ-treated AD mice decreased significantly compared with sham mice in the presence of neuronal atrophy, while intraperitoneal injection of Dex led to a marked elevation in Nissl body number in AD mouse hippocampus and an obvious reduction in neuronal atrophy. Moreover, the MWM test of mouse learning and memory ability in each group showed that the escape latency of AD mice in the Dex group was significantly shortened compared with the Aβ group, with a statistically significant higher number of platform crossings and target quadrant residence time, suggesting significantly reduced cognitive dysfunction in AD mice after Dex treatment. Considering the aforementioned inhibitory effect of Dex on ferroptosis of HNs in mice, it can be concluded that Dex can extend the survival of neurons by inhibiting HN ferroptosis, thus improving cognitive function in AD mice.

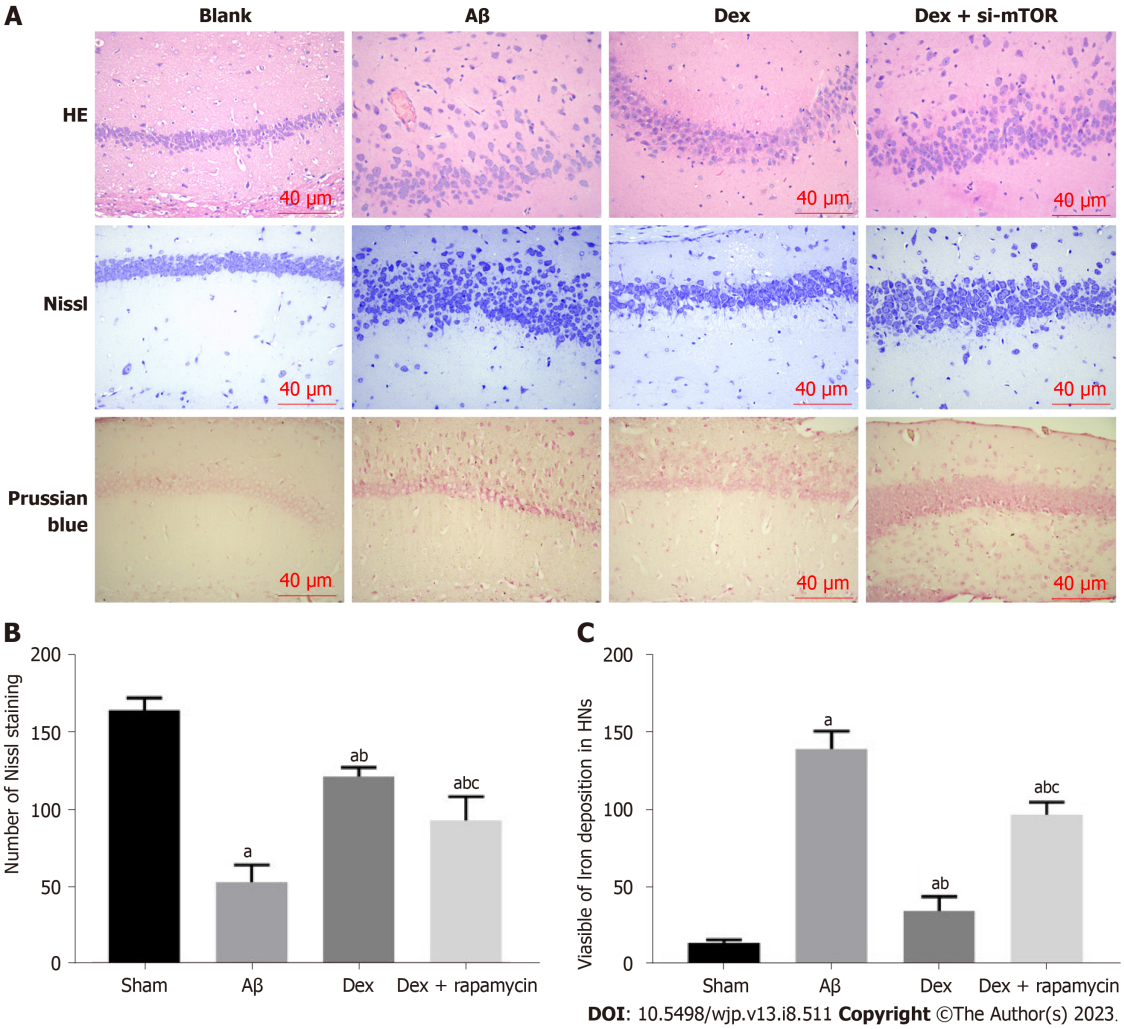


Figure 5 Comparison of pathological changes, nerve cell injury and iron deposition in mouse brain tissue in the different treatment groups. A: Hematoxylin and eosin, Nissl, and Prussian blue staining for pathological changes, neuronal damage, and iron deposition in the brain tissue of mice in each group. Scale bar, 40 μm; B: Representative photomicrographs of Nissl staining of surviving neurons in the hippocampal region, and statistical analysis of Nissl bodies in each group; C: Representative photomicrographs of Prussian blue staining of surviving neurons in the hippocampal region, and statistical analysis of iron deposition in each group. $^{a}P < 0.05$, compared with the sham group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; si-mTOR: Mammalian target of rapamycin siRNA; HE: Hematoxylin and eosin; HNs: Hippocampal neurons.

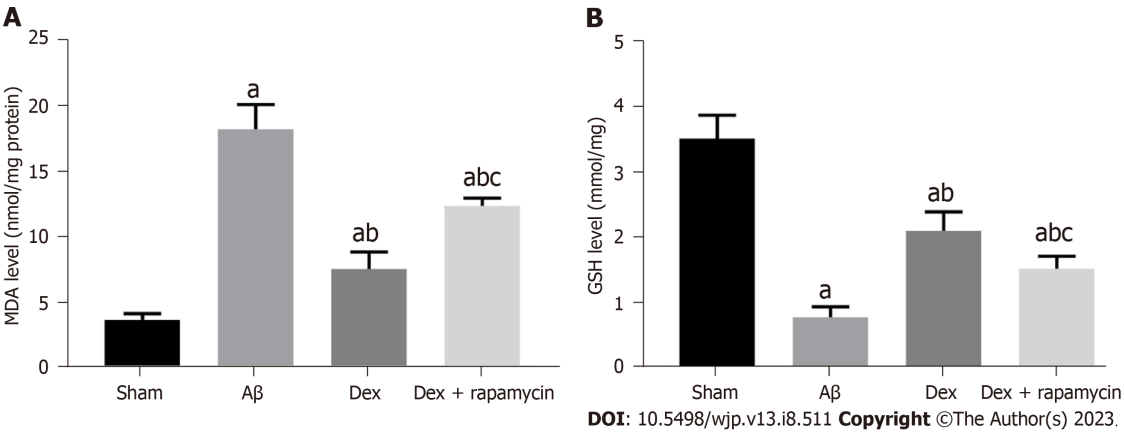


Figure 6 Comparison of oxidative stress index levels in mouse brain tissue in the different treatment groups. A: Absorbance of the oxidation reaction was measured to evaluate the cellular malondialdehyde level using kits; B: The activity levels of glutathione enzyme activity was measured using kits according to a colorimetric method. $^{a}P < 0.05$, compared with the sham group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; MDA: Malondialdehyde; GSH: Glutathione.

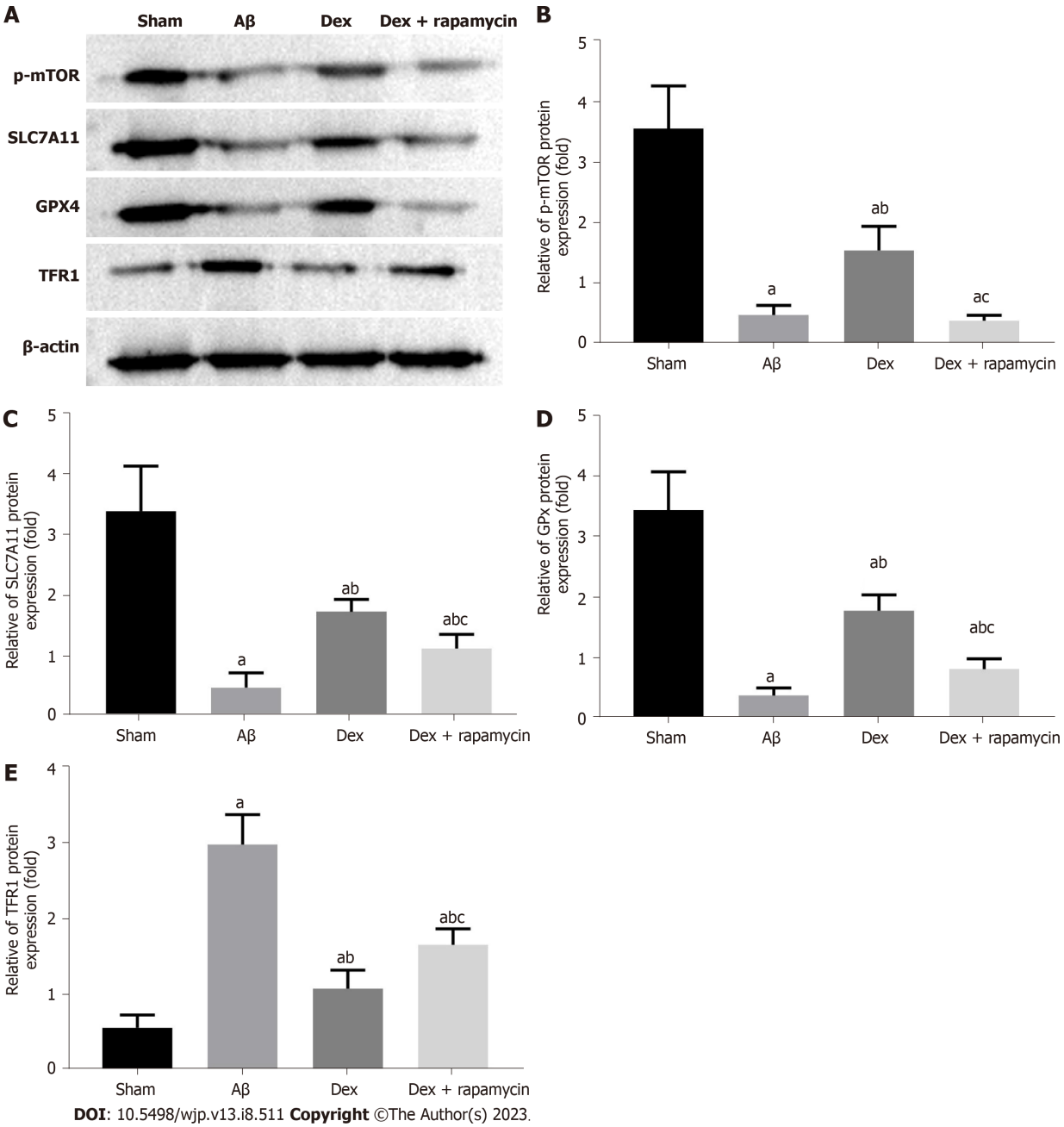


Figure 7 Comparison of iron death-related protein levels in mouse brain tissue in the different treatment groups. A: Expression levels of p-mammalian target of rapamycin, SLC7A11, glutathione peroxidase 4, and transferrin receptor 1 in mouse brain tissue were detected by western blot; B-E: The relevant data. $^{a}P < 0.05$, compared with the sham group; $^{b}P < 0.05$, compared with the amyloid β group; $^{c}P < 0.05$, compared with the dexmedetomidine group. Aβ: Amyloid β; Dex: Dexmedetomidine; mTOR: Mammalian target of rapamycin; GPX4: Glutathione peroxidase 4; TFR1: Transferrin receptor 1.

The mTOR axis has been reported to play a regulatory role in cell death and apoptosis in various diseases such as aging, NDDs, and brain injury[26]. Increasing attention has recently been paid to the mechanism of mTOR mediated ferroptosis. It has long been reported that mTOR plays a regulatory role in upstream targets of iron metabolism, and that the mTOR-TFR1 axis is essential in balancing iron homeostasis by regulating TFR1 expression[27]. Our experimental results revealed that inhibition of the mTOR pathway significantly promoted Fe^{2+}, OS and TFR1 levels in mouse HNs, and lowered GPX4 and SLC7A11 expression, indicating that the ability of Dex to protect HNs from Aβ-induced ferroptosis and mitigate cognitive dysfunction in AD mice is weakened following inhibition of mTOR expression. It is suggested that Dex can reduce ferroptosis of HNs and ease cognitive dysfunction in AD mice, possibly by activating the mTOR axis.

CONCLUSION

Both *in vitro* and *in vivo* experiments in this study confirmed that Dex can inhibit Aβ-induced ferroptosis of mouse HNs, and effectively reduce HN loss and cognitive dysfunction in AD mice. Furthermore, Dex improved learning and memory

in AD mice by modulating the mTOR-TFR1 axis to reduce ferroptosis.

ARTICLE HIGHLIGHTS

Research background

The main pathological feature of Alzheimer's disease (AD) is the formation of amyloid β-protein (Aβ) plaques in the brain, leading to loss of neuronal synapses, ultimately affecting the patient's learning and memory abilities. Research has shown that iron death caused by iron overload in nerve cells is an important factor leading to neurodegenerative diseases, and plays a crucial role in the progression of AD. Recently, reports have demonstrated the high selectivity of dexmedetomidine (Dex), an α adrenergic receptor agonist, that can exert neuroprotective effects by inhibiting the release of inflammatory factors, thereby improving cognitive dysfunction in elderly rats.

Research motivation

Currently, there are still no effective drugs to delay the progression of AD, and iron death which may play a crucial role in the progression of this disease is attracting increasing attention from researchers.

Research objectives

To investigate the effect of Dex on iron death in the hippocampus of AD mice by both *in vitro* and *in vivo* research.

Research methods

Construction and utilization of an AD model using Aβ. The mouse hippocampal neuronal cell line HT22 was induced, and the levels of cell proliferation activity and intracellular Fe^{2+} were measured by the cell-counting kit-8 assay and immunofluorescence. The contents of malondialdehyde and glutathione were measured by the TBA method and microplate method, respectively. In the AD mouse model Aβ was injected, and the pathological damage in the mouse hippocampus was detected by hematoxylin and eosin staining and Nissl staining. The Morris water maze was used to evaluate the learning and memory abilities of mice in each group, and protein immunoblotting was used to evaluate the expression levels of p-mammalian target of rapamycin (p-mTOR) and iron death-related proteins transferrin receptor 1 (TFR1), SLC7A11, and glutathione peroxidase 4.

Research results

Dex significantly improved lipid peroxidation and iron influx in mouse hippocampal neurons (HNs) both *in vivo* and *in vitro*, and inhibition of the mTOR signaling pathway blocked this process, demonstrating that Dex can inhibit the damage caused by iron death in mouse HNs by activating mTOR-TFR1 signaling regulation, thereby improving cognitive dysfunction in AD mice.

Research conclusions

Dex can significantly activate the mTOR-TFR1 signaling pathway and inhibit iron death in mouse HNs, thereby improving the learning and memory abilities of mice.

Research perspectives

From *in vitro* and *in vivo* molecular experimental research, it is possible to analyze the effect of Dex on iron death in AD related nerve cells.

FOOTNOTES

Author contributions: Qiao L and Yuan HX conceived the study design and the content concept; Li G and Yuan HX performed data collection, extraction and analysis, interpreted and reviewed the data and drafts; Qiao L, Li G, and Yuan HX reviewed the final draft. Li G and Yuan HX are co-corresponding authors with equal contribution to the article.

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ORIGINAL ARTICLE

Basic Study

Pilot study of genome-wide DNA methylation and gene expression for treatment response to escitalopram in panic disorder

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Abstract

BACKGROUND

Antidepressants, particularly selective serotonin reuptake inhibitors, are currently considered the first-line treatment for panic disorder (PD). However, little is known about the relationship between the biomarkers that may predict better treatment.

AIM

To compare genome-wide methylation and gene expression patterns between responsive and non-responsive patients with PD after 4 wk of escitalopram treatment.

METHODS

Thirty patients with PD were enrolled in this study (responders = 13; non-responders = 17). All patients were assessed using the PD Severity Scale-Chinese version before and after treatment. The Illumina Infinium MethylationEPIC (850k) BeadChip for genome-wide methylation screening and mRNA sequencing was used in all patients with PD.

RESULTS

A total of 701 differentially methylated positions (DMPs) were found between responders and non-responders ($|\Delta\beta| \geq 0.06$, $q < 0.05$), and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively. Relative to non-responders, there were 59 differential transcripts, of which 20 were downregulated and 39 were upregulated ($q < 0.05$). However, no differen-

tially expressed genes were identified by mRNA sequencing after correcting for multiple testing (|log2(FC)| > 1, q > 0.05).

CONCLUSION

This preliminary study showed that DMPs might be associated with the treatment response to escitalopram in PD; however, these DMPs need to be verified in large samples.

Key Words: Panic disorder; Methylation; Expression profiling; Escitalopram

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Core Tip: No genome-wide methylation studies or mRNA sequencing have been conducted to identify early response biomarkers in patients with panic disorder (PD). This study aimed to compare genome-wide methylation and gene expression patterns between responsive and non-responsive patients with PD after 4 wk of escitalopram treatment. A total of 701 differentially methylated positions (DMPs) were found between responders and non-responders, and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively. This preliminary study showed that DMPs might be associated with the treatment response to escitalopram in PD.

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INTRODUCTION

Panic disorder (PD) is a common anxiety disorder characterized by recurrent and unexpected panic attacks. The estimated 12-month and lifetime prevalences of PD are 2.4% and 3.8%, respectively[1,2]. A cross-national epidemiological study reported that the lifetime prevalence of panic attacks was 13.2%[3]. Patients with PD experience symptoms such as tachycardia, chest pain, breathlessness, and dizziness. Consequently, they most frequently seek care in medical settings, such as emergency departments, and their condition is often undiagnosed[4]. PD causes substantial suffering and increases economic costs for both patients and society[5]. Hence, the availability of effective treatment may not only benefit individual patients but also provide economic returns to society.

Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are currently considered first-line treatments for PD. A meta-analysis suggested that SSRIs result in high remission rates with a minimal risk of adverse events in the treatment of PD[6,7]. However, not all patients benefit from the antidepressant therapy. For example, in a 12-week clinical trial of sertraline, citalopram, escitalopram, and paroxetine, 11.1%–18% of patients with PD did not respond to treatment[8,9]. Thus, predictive biomarkers of antidepressant response could greatly benefit clinical practice by decreasing the duration of drug efficacy evaluations.

Previous studies have found that common genetic variants could explain 42% of the individual differences in antidepressant response[10]. In addition, gene polymorphism studies focusing on *5-HTT*, *5-HTR1A*, *5-HTR2A*, *COMT*, *BDNF*, and *P450* (*CYP*) have been conducted in several large-scale studies on antidepressant drug responses in PD[11-14]. However, no consistent findings have been obtained from these studies. For example, with regard to treatment response to SSRIs in patients with PD, Zou *et al*[13] found that *5-HTTLPR* polymorphism, rather than *5-HTR1A*, may be an early predictor of response to sertraline in 2020, whereas Yevtushenko *et al*[11] indicated the importance of a *5-HT1A* receptor gene polymorphism in 2010. Therefore, genetic variation in a single gene cannot fully explain individual differences in the response to treatment.

Emerging evidence from human and animal studies suggests a key role of epigenetic markers, including DNA methylation and histone modifications, in the prediction of antidepressant response[15]. Methylation of some candidate genes, such as *SLC6A4*, *BDNF*, and *IL11*, has shown promising results as a biomarker for predicting antidepressant responses in major depressive disorder (MDD). However, the research methods and results have been heterogeneous [16]. Genome-wide methylation analysis can accurately determine the location of DNA methylation in the genome and screen for effect-related differentially methylated genes. Currently, 850k methylation BeadChip is a new generation of DNA methylation chips developed based on the original 450k methylation chip[17]. The newly developed Human Methylation 850 BeadChip covers over 850k CpG methylation sites and is the most useful tool for analyzing the DNA methylation profile of the human genome. In addition, DNA methylation is a key epigenetic mechanism involved in the developmental regulation of gene expression[18]. Nevertheless, no genome-wide methylation studies or mRNA sequencing have been conducted to identify early response biomarkers in patients with PD.

Hence, a pilot study of genome-wide DNA methylation and gene expression analysis was conducted in patients with PD using the Illumina 850k BeadChip and mRNA sequencing to identify possible predictors of treatment response to escitalopram.

MATERIALS AND METHODS

Study sample

All patients with PD were recruited from the inpatient and outpatient departments of Sichuan Provincial People's Hospital between March 2019 and December 2020. All patients satisfied the following inclusion criteria: (1) Primary diagnosis of PD in line with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) performed by a professional psychiatrist through a standardized structured clinical interview for DSM-IV Axis I disorders[19], with none of the patients having any other psychiatric disorders; (2) All PD patients were medication-naïve and had no history of any antidepressant or other psychotropic medication intake; (3) All subjects were without suicide ideations and attempts; (4) Subjects had no family history of psychiatric disorders in a first-degree relative; (5) All patients were Han Chinese aged 18 to 60 years; (6) All subjects were free of acute or chronic somatic disorders, head trauma, or neurological illnesses, and all subjects were free of alcohol consumption within 2 wk before their examination. Women were non-pregnant and non-nursing; and (7) All patients received escitalopram (10–20 mg qd) for 4 wk. The study was approved by the Sichuan Provincial People's Hospital ethics committee [reference number: (2021) Ethics Review (313)]. All individuals provided written informed consent prior to the initiation of study procedures.

Clinical assessment

Patients were assessed at baseline and after 4 wk of treatment using the PD Severity Scale (PDSS). The PDSS comprises seven items, and participants are instructed to rate each item from 0 (none) to 4 (extremely severe) based on the severity of each symptom[20]. The PDSS-Chinese version has good internal consistency (Cronbach's alpha) with an overall score of 0.83[21]. Treatment response for PD was defined as a reduction in the pretreatment PDSS score of at least 40% at 4 wk [22]. The PD samples were divided into responder and non-responder groups.

DNA and RNA extraction

A 4-mL ethylenediaminetetraacetic acid-anticoagulated peripheral blood sample was collected from all subjects in a fasting state *via* venipuncture between 7:00 a.m. and 8:30 a.m. DNA and RNA were extracted from whole blood samples from PD patients at baseline using DNeasy Blood and miRNeasy Mini kits (Qiagen, Hilden, Germany), respectively, according to the manufacturer's protocol.

Genome-wide DNA methylation analysis

DNA was subjected to sodium bisulfite conversion using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA, United States). The Illumina Infinium Human Methylation 850K BeadChip (Illumina, San Diego, CA, United States) was used to assess genome-wide DNA methylation, with a genome-wide coverage of over 850k CpG methylation sites per sample according to the manufacturer's instructions. DNA quality control, bisulfite conversion, genome-wide methylation analysis, and initial methylation signal detection quality control were performed by Sinotech Genomics Co., Ltd. (Shanghai, China).

The raw intensity data were imported into R (v4.0.0; R Foundation for Statistical Computing, Vienna, Austria) and analyzed using the ChIP (ChAMP) package (v2.18.2) for data preprocessing, normalization, and comparison. β-values (ranging from 0 to 1) were used to determine the DNA methylation levels at each CpG site. Probes were filtered, including probes with a detection p-value of < 0.01, probes with less than three beads in at least 5% of the samples, non-CpG probes, and multi-hit probes. Beta-Mixture Quantile was used to normalize β-value matrices to adjust for type I and II probe biases[23]. In addition, we used singular value decomposition analysis to analyze the batch effect caused by the BeadChip Slide and Array and applied Combat to correct this batch effect[24]. Finally, all CpG sites were annotated using EPICanno software. ilm10b5. hg19.

Gene expression analysis

An Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, United States) was used to assess RNA quality. A Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA, United States) and NanoDrop One spectrophotometer (Thermo Fisher Scientific) were used to quantify total RNA, after which the library was constructed. The library for polymerase chain reaction product purification by paired-end libraries was synthesized using the mRNA-seq Lib Prep Kit for Illumina (ABclonal, Wuhan, China) following the sample preparation guide. Libraries were quantified using a Qubit® 3.0 Fluorometer (Thermo Fisher Scientific) and validated using an Agilent 2100 Bioanalyzer (Agilent Technologies) to calculate the molar concentration and insert size. Clusters were generated using the cBot user guide and sequenced using an Illumina NovaSeq 6000 system (Illumina). Library construction and sequencing were performed by Sinotech Genomics Co. Ltd.

Hisat2 (2.1.0) was used to map the paired-end sequence files (fastq) to the reference genome (GRCh38.91). The output sequencing alignment/map files were converted into binary alignment/map files and sorted using SAM tools (v1.7). Gene abundance was expressed as fragments per kilobase of exons per million reads mapped (FPKM). StringTie software was used to count the fragments within each gene, and the TMM algorithm was used for normalization (https://www.ncbi.nlm.nih.gov/COG/). Finally, the FPKM value of each gene was calculated. EdgeR software was used to conduct differential expression analysis of the mRNA[25].

Statistical analysis

Data were analyzed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, United States). Intergroup comparisons of continuous variables were conducted using Student's t-test, and categorical variables were analyzed using Pearson's chi-

square test. Differentially methylated CpG positions were identified using ChAMP. Δβ was calculated as the difference of mean β-values between responders and non-responders. We set the criteria for differential methylation positions (DMPs) as the calling significance of an absolute change in Δβ-value between groups ($|\Delta\beta| \geq 0.06$ and $q < 0.05$). Differentially expressed mRNAs were defined as $|\log2(FC)| > 1$ and $q < 0.05$. To identify genes with the same function and pathway in DNA methylation and gene expression profiling, we performed gene ontology (GO) (http://geneontology.org/) analysis for biological processes, cellular components, and molecular function, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis (http://www.kegg.jp/) for differentially methylated and expressed genes. For all statistical analyses, a two-tailed p-value < 0.05 indicated statistical significance. The q-value cut-off of 0.05 was corrected using the Benjamini–Hochberg method for multiple hypotheses[26].

RESULTS

Demographic and clinical characteristics

PD samples were divided into 13 responders (6 men and 7 women; 33.54 ± 11.64 years old) and 17 non-responders (8 men and 9 women; 33.88 ±9.65 years old) at 4 wk. No statistically significant differences were found between the responders and non-responders in terms of sex ($\chi^2 = 0.002$, $p > 0.05$) or age ($t = -0.088$, $p > 0.05$). There were 4 smokers (30.8%) and 9 nonsmokers (69.2%) in the responder group, and 5 smokers and 12 nonsmokers in the non-responder group. The number of drinkers and nondrinkers among the responders was 3 (23.1%) and 10 (76.9%) in the responder group, and 5 drinkers and 12 nondrinkers in the non-responder group. No statistically significant group difference was observed in terms of smoking and drinking ($\chi^2 = 0.006$, 0.151; $p > 0.05$). In addition, the average PDSS total score was 13.08 ± 4.25 in responders and 14.94 ± 3.25 in non-responders at the start of treatment, and no statistically significant group difference was observed ($t = -1.363$, $p > 0.05$). The average PDSS total score for responders was 4.54 ± 2.11, which was significantly lower than that for non-responders 10.35 ± 2.00 after 4 wk of treatment ($p < 0.001$).

Differential methylation analysis

Compared with non-responders, there were 701 DMPs ($|\Delta\beta| \geq 0.06$, $q < 0.05$), and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively (Supplementary Table 1). The distribution of DMPs in the CpG islands was as follows: N-shore (34.6%), S-shore (24.5%), N-shelf (16.5%), island (14.4%), and S-shelf (10.1%). These DMPs in different regions of the gene were in the following order: Body region (64.4%), transcriptional start site (TSS) 1500 (15.3%), 5′-untranslated region (UTR) region (12.5%), 1st Exon (3.4%), TSS 200 (3.1%), and the 3′-UTR region (1.3%). According to the University of California Santa Cruz annotation, 437 unique genes were identified, including 311 hypermethylated and 122 hypomethylated genes; the coexistence of hyper- and hypomethylation sites was found in four genes (Supplementary Table 2).

Enrichment analysis of differentially methylated genes

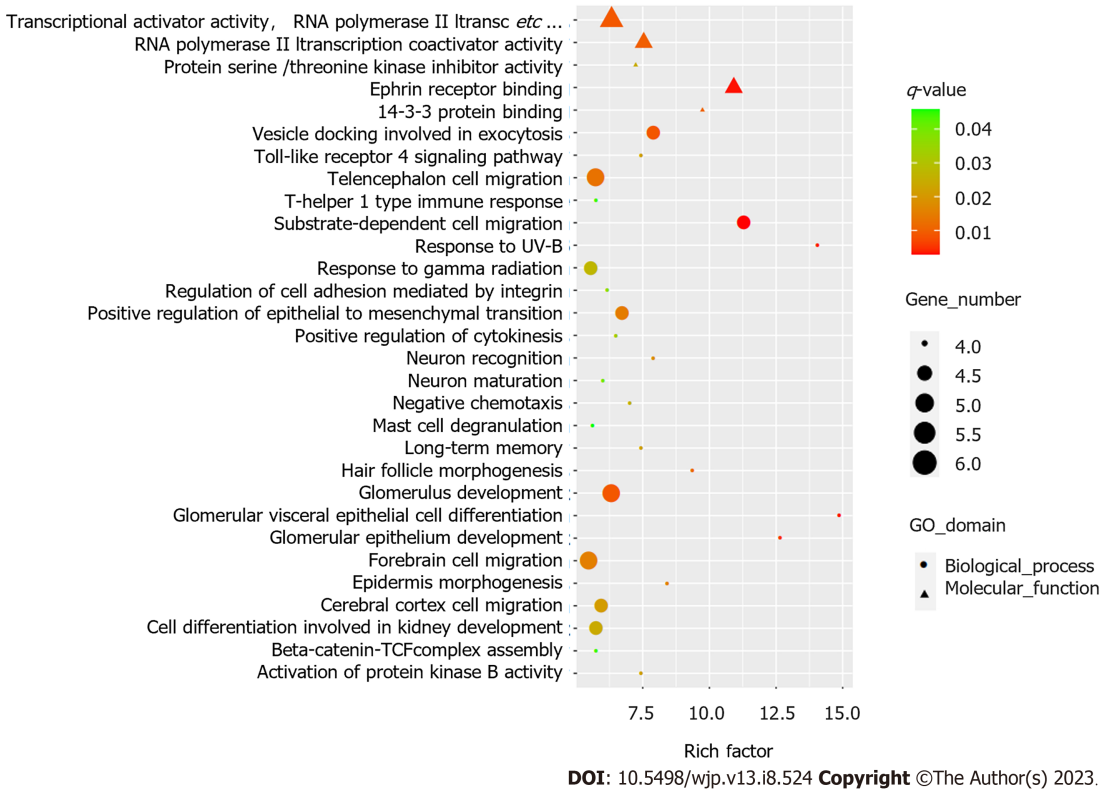
GO analysis revealed distinct functional categories for the associated genes, and approximately 226 biological processes, 14 cellular components, and 22 molecular functions were identified in differentially methylated genes ($q < 0.05$). Figure 1 shows the top 30 GO annotations for the differentially methylated genes. KEGG analysis showed that these differentially methylated genes were involved in 43 significant pathways ($p < 0.05$). However, no statistically significant pathways were found after adjusting using the Benjamini–Hochberg method ($q > 0.05$) (Supplementary Table 3).

Differential mRNA expression analysis

Compared with non-responders, there were 59 differential transcripts after adjusting using the Benjamini–Hochberg method, of which 20 were downregulated and 39 were upregulated ($q < 0.05$) (Figure 2). After the data were analyzed using the screening procedure, the results of mRNA sequencing showed that 132 differentially expressed genes were identified ($p < 0.05$). However, no statistically significant group differences between responders and non-responders were observed after adjusting using the Benjamini–Hochberg method ($q > 0.05$) (Supplementary Table 4).

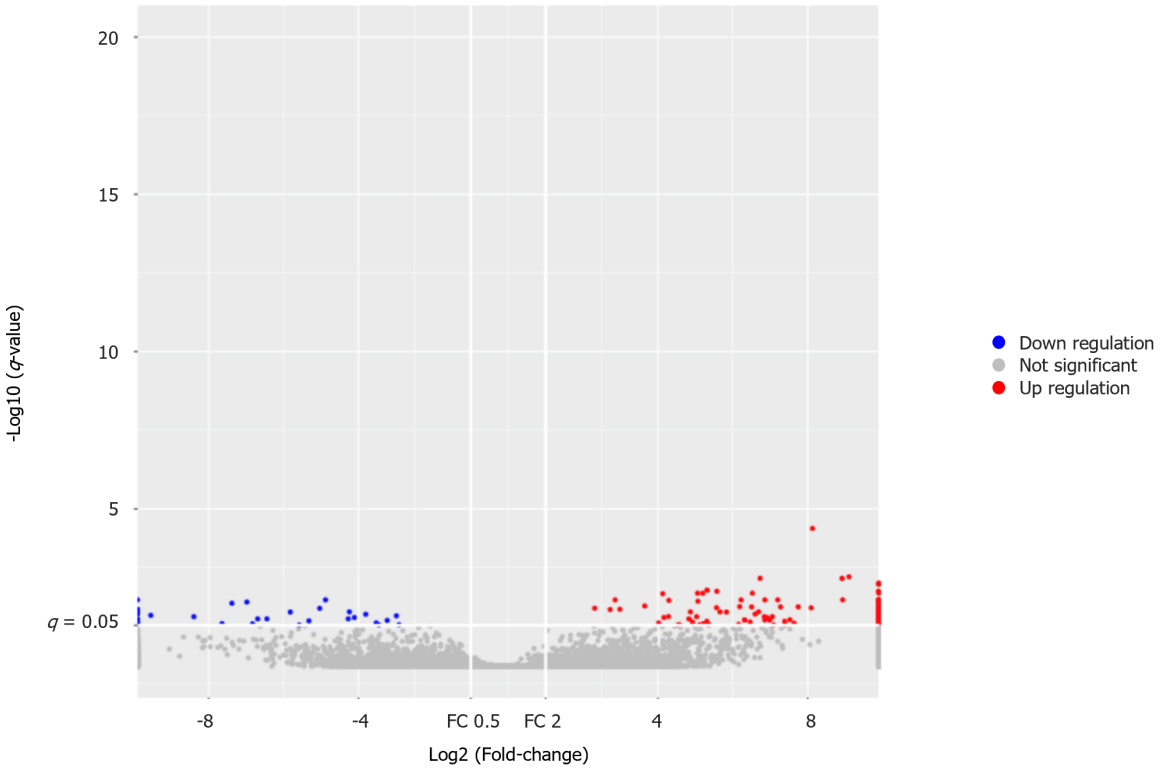
DISCUSSION

DNA methylation plays an important role not only in the diagnosis of diseases but also in the prediction of efficacy[16, 27]. In this study, a pilot investigation of genome-wide DNA methylation in the early response to antidepressants in patients with PD was conducted using the Illumina 850k BeadChip. To our knowledge, this is the first genome-wide DNA methylation study of the treatment response to escitalopram in PD. According to the screening criteria for differential methylation sites, 701 DMPs were screened among responders and non-responders in patients with PD, and these DMPs were located within 437 unique genes. Similarly, one study assessed genome-wide DNA methylation using the Infinium MethylationEPIC BeadChip in patients with MDD for escitalopram treatment response. They identified 2571 significant DMPs, and 303 DMPs with an absolute change in Δβ-value between groups larger than 0.2[28]. These findings indicate that DMPs are potential peripheral predictors of antidepressant treatment response, and present an important opportunity to improve symptoms through prediction of medication response. Not only that, there is also some emerging evidence to suggest that PD patients have aberrant DNA methylations[29]. Psychiatry as a medical discipline, a diagnosis identifying a disorder should lead to an effective therapy[30]. Hence, epigenetic factors contributing to antidepressant



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Figure 1 Top 30 of gene ontology enrichment in differentially methylated genes. GO: Gene ontology.



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Figure 2 Differential transcripts between responders and non-responders.

response will be a unique and promising opportunity to implement personalized medicine in PD treatment. In addition, in the present study, most DMPs with an absolute change in value between groups were lower than 0.1. Furthermore, Ju *et al*[28] found that many DMPs showed very small differences in methylation (Δβ < 0.5%), making it difficult to fully

explain efficacy prediction from a single CpG site. The treatment efficacy may be largely determined by the combined effects of multiple loci.

Notably, the current study identified 10 DMPs with an absolute change in Δβ-value larger than 0.2 ($|\Delta\beta| \geq 0.2$) between groups, and these genes included *HLA-DPB1*, *HLA-DPA1*, *PDE1A*, *COL23A1*, *RUFY4*, *FRMD5*, and *SOHLH1*. For example, the *HLA-DPB1* site (cg12865025) is located in the TSS 1500 region. The major histocompatibility complex class II molecule consists of non-covalently associated alpha and beta chains, and this class II molecule is a heterodimer consisting of an alpha (DPA) and a beta chain (DPB)[31]. *HLA-DPA1* and *HLA-DPB1* are expressed on the surfaces of antigen-presenting cells; they play a central role in the adaptive immune system[32] and are associated with the pathophysiology of psychiatric disorders[17]. In recent years, increasing evidence has suggested that aberrations in immune-related pathways contribute to the pathophysiology and prediction of treatment responses in patients with PD [33,34]. Moreover, escitalopram led to a decrease in immune system activation[35], augmented tumor necrosis factor-peripheral secretion, induced faster kinetics of interleukin-1β secretion[36], and decreased Interleukin-17 levels[37]. Therefore, immune-related pathways may play an important role in the response to antidepressants in patients with PD. However, whether these DMPs can be used as molecular markers needs to be verified in larger samples.

In this study, functional enrichment analysis of differentially expressed genes was performed. GO analysis identified 262 GO terms in differentially methylated genes. Notably, the top 30 GO annotations, such as neuron recognition, neuron maturation, and cerebral cortex cell migration, may be associated with the treatment response. These enriched genes, including *DAB1*, *NRP1*, *DIXDC1*, *ROBO1*, *PEX5*, *APP*, *ANKS1A*, *EDNRB*, *BCL2*, and *NTM*, play central roles in brain development, neuronal remodeling, neurite outgrowth, and adhesion. For example, antidepressants such as citalopram increase *APP* secretion in primary rat neuronal cultures[38]. In addition, previous findings suggest that citalopram reduces mutant *APP*, Aβ, and mitochondrial toxicities and may have a protective role against mutant *APP* and Aβ-induced injuries in patients with depression, anxiety, and Alzheimer's disease[39]. In addition, these genes have a potential role in the development of many neuropsychiatric diseases. For example, a previous study found that *Dab1* knockout mice exhibited behavioral abnormalities, including hyperactivity, decreased anxiety-like behavior, and impaired working memory[40]. Hence, these differentially methylated genes in the GO terms may be involved in the pathophysiology and therapeutic response in PD, and the functions of these genes need further exploration. Further studies are needed to explore whether differential methylation in peripheral blood is similar to that in the brain.

Few studies have explored the association between gene expression and the prediction of therapeutic response in patients with PD. In this study, mRNA sequencing was compared between responders and non-responders among patients with PD. Unfortunately, no statistically significant group differences were found in differentially expressed genes. Furthermore, no candidate genes were identified based on integrative analysis of differential DNA methylation and expression. This may be due to the following reasons. First, the sample size was small. The different clinical features of patients with PD are closely related to the heterogeneity of heredity. Second, the use of whole blood, which is a mixed cell type sample, may limit the identification of mRNA expression changes. Finally, gene expression is affected by many factors, such as environmental and other epigenetic factors, especially non-coding RNA, which represents a promising source of peripheral biomarkers of antidepressant responses[41]. Ultimately, it is likely that combinations and not individual biomarkers will have the greatest utility in predicting antidepressant responses. In the future, researchers should integrate multiple types of information, including genetic, epigenetic, and gene expression data, to identify the most meaningful panel of biomarkers.

CONCLUSION

In conclusion, this preliminary study showed that DMPs may be associated with an early response to antidepressants in patients with PD. However, the results of our study should be considered in light of the following limitations. Since this is the first study to investigate genome-wide DNA methylation and gene expression in the prediction of early response to antidepressants in PD, it would be valuable to replicate our findings in a larger cohort. Furthermore, these DMPs must be verified using larger sample sizes. Lastly, it is necessary to test the association between treatment outcomes and changes in DNA methylation and gene expression from pre- to post-treatment with a long-term follow-up.

ARTICLE HIGHLIGHTS

Research background

Selective serotonin reuptake inhibitors are currently considered the first-line treatment for panic disorder (PD). However, not all patients benefit from the antidepressant therapy.

Research motivation

No genome-wide methylation studies or mRNA sequencing have been conducted to identify early response biomarkers in patients with PD.

Research objectives

To compare genome-wide methylation and gene expression patterns between responsive and non-responsive patients with PD after 4 wk of escitalopram treatment.

Research methods
Thirty patients with PD were enrolled in this study (responders = 13; non-responders = 17). All patients were assessed using the PD Severity Scale-Chinese version before and after treatment. The Illumina Infinium MethylationEPIC (850k) BeadChip for genome-wide methylation screening and mRNA sequencing was used in all patients with PD.

Research results
A total of 701 differentially methylated positions (DMPs) were found between responders and non-responders ($|\Delta\beta| \geq 0.06$, $q < 0.05$), and the hyper- and hypomethylated CpG sites were 511 (72.9%) and 190 (27.1%), respectively. Relative to non-responders, there were 59 differential transcripts, of which 20 were downregulated and 39 were upregulated ($q < 0.05$).

Research conclusions
This preliminary study showed that DMPs might be associated with the treatment response to escitalopram in PD, however, these DMPs need to be verified in large samples.

Research perspectives
DNA methylation contributing to antidepressant response will be a unique and promising opportunity to implement personalized medicine in PD treatment.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Effects of surgical treatment modalities on postoperative cognitive function and delirium in elderly patients with extremely unstable hip fractures

Xue Zhou, Xiao-Hua Chen, Sheng-Hua Li, Nan Li, Feng Liu, Hao-Ming Wang

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Abstract

BACKGROUND

As the perioperative risk of elderly patients with extremely unstable hip fractures (EUHFs) is relatively high and therapeutic effect is not satisfactory, new therapeutic strategies need to be proposed urgently to improve the efficacy and clinical outcomes of such patients.

AIM

To determine the influence of two surgical treatment modalities on postoperative cognitive function (CF) and delirium in elderly patients with EUHFs.

METHODS

A total of 60 elderly patients consecutively diagnosed with EUHF between September 2020 and January 2022 in the Chongqing University Three Gorges Hospital were included. Of them, 30 patients received conventional treatment (control group; general consultation + fracture type-guided internal fixation), and the other 30 received novel treatment (research group; perioperative multidisciplinary treatment diagnosis and treatment + individualized surgical plan + risk prediction). Information on hip function [Harris hip score (HHS)], perioperative risk of orthopedic surgery [Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM)], CF [Montreal cognitive assessment scale (MoCA)], postoperative delirium [mini-cognitive (Mini-Cog)],

adverse events (AEs; internal fixation failure, infection, nonunion, malunion, and postoperative delirium), and clinical indicators [operation time (OT), postoperative hospital length of stay (HLOS), ambulation time, and intraoperative blood loss (IBL)] were collected from both groups for comparative analyses.

RESULTS

The HHS scores were similar between both groups. The POSSUM score at 6 mo after surgery was significantly lower in the research group compared with the control group, and MoCA and Mini-Cog scores were statistically higher. In addition, the overall postoperative complication rate was significantly lower in the research than in the control group, including reduced OT, postoperative HLOS, ambulation time, and IBL.

CONCLUSION

The new treatment modality has more clinical advantages over the conventional treatment, such as less IBL, faster functional recovery, more effectively optimized perioperative quality control, improved postoperative CF, mitigated postoperative delirium, and reduced operation-related AEs.

Key Words: Extremely unstable hip fracture; Elderly; Multidisciplinary treatment; Cognitive function; Postoperative delirium

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Core Tip: Characterized by severe fragmentation, extreme instability, and treatment-refractory, extremely unstable hip fractures (EUHFs) in the elderly population carry a higher perioperative risk. Given the unsatisfactory treatment outcomes of EUHFs in the elderly, there is an urgent need to develop new therapeutic strategies to improve the efficacy and clinical outcomes in these patients, thus providing a guarantee for their life, health, and quality of life.

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INTRODUCTION

Extremely unstable hip fractures (EUHFs) account for approximately one-fourth of all hip fractures, mainly including Garden grade III and IV fractures of the femoral neck, A2 and A3 intertrochanteric femur fractures, and Seinsheimer type III and IV subtrochanteric femoral fractures, characterized by severe fragmentation, extreme instability, and treatment-refractory[1,2]. EUHF has a predilection for two groups of people: Young people who have suffered major trauma and elderly people with severe osteoporosis and minor trauma[3]. Elderly patients with EUHF have a higher perioperative risk due to their poorer physical conditions than young and middle-aged people and the high likelihood of comorbidities such as hyperlipidemia, hyperglycemia, hypertension, and other internal diseases[4]. Clinically, the surgical treatment modality for elderly patients with EUHF is selected mainly on the fracture type, which not only leads to unsatisfactory treatment outcome but may also cause postoperative cognitive dysfunction in > 40% and postoperative delirium in 5%-61% of patients, severely affecting their quality of life (QoL)[5,6]. Therefore, it is imperative to develop novel treatment strategies to improve the efficacy and clinical outcomes in elderly patients with EUHF and to provide a guarantee for their life, better health, and improved QoL.

Multidisciplinary treatment (MDT) is a diagnosis and treatment model that gathers the backbones of EUHF-related departments, such as geriatrics, critical medicine, anesthesiology, mental health, and rehabilitation medicine, to tailor personalized examination and treatment plans for patients to improve patient diagnosis and treatment experience and enhance treatment efficacy[7-9]. A randomized controlled trial including elderly patients with hip fractures also observed significant improvement in postoperative clinical outcomes using MDT, which suggested that MDT has great application potential in elderly patients with EUHF[10]. On the other hand, anatomic reduction, internal fixation, and effective control of postoperative adverse events (AEs) for EUHFs are the keys to successful surgery due to the vulnerability to fractures of the area involved and the complexity and involvement of the surrounding muscle groups[11,12]. We believe that individualized customization + fracture type co-determined internal fixation is a feasible and safe program, and risk prediction and advance treatment through Mini-Cog plus orthopedic Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) scale assessment can further help minimize the surgical risks.

To test our conjecture and supplement the evidence-based new treatment model (MDT diagnosis and treatment + individualized surgical plan + risk prediction) still lacks, this study compared the clinical effects of the two surgical treatment modalities through a clinical cohort study to optimize and scientifically guide the clinical treatment.

MATERIALS AND METHODS

General data

This study comprised 60 elderly patients diagnosed consecutively with EUHF in the Chongqing University Three Gorges Hospital between September 2020 and January 2022. Of 60, 30 patients were treated using the conventional treatment model of general consultation plus fracture type-guided internal fixation (control group), and the other 30 patients received a new treatment model of perioperative MDT diagnosis and treatment + individualized surgical plan + risk prediction (research group). The two patient groups had similar baseline data ($P > 0.05$), which was clinically comparable.

Inclusion and exclusion criteria for patient enrollment

Patients diagnosed with extremely unstable femoral intertrochanteric fractures (Garden grade III or IV fractures of the femoral neck, A2 or A3 intertrochanteric femur fractures, or Seinsheimer type III or type IV subtrochanteric femoral fractures), but not old or pathological fractures, using computed tomography, magnetic resonance imaging, and other imaging examinations[13,14], with no severe osteoporosis, t value ≥ -2.5, normal communication and cognitive abilities, and active cooperation were included.

The exclusion criteria were as follows: Other hip diseases; serious nerve; vascular or muscle injuries; other joint diseases; femoral head necrosis; serious infections; diseases such as coagulation dysfunction, cardiopulmonary disease, and renal failure; drug and alcohol addiction; and history of severe trauma around the hip joint.

Treatment protocols

The control group received conventional treatment, with the following specific measures: Post-admission general consultation was provided to the patients and relevant examinations and treatment were further conducted according to the consultation. The patient's underlying diseases were stabilized preoperatively; however, another preoperative evaluation was conducted by the anesthesiologist. The surgical protocol was selected depending on the patient's fracture type. After surgery, the patient's vital signs, mental state, food intake, blood routine, biochemical indexes, drainage volume, and cardiopulmonary function were obtained, and bilateral lower limb vascular ultrasonography was performed. Prophylactic antibiotics were used within 24 h after surgery, and anticoagulant therapy composed of low molecular weight heparin and rivaroxaban was routinely given. Postoperatively, the affected limb was raised according to the patient's fracture type, surgical condition, and general condition. In addition, the patient was instructed to perform quadriceps isometric contraction and ankle pump exercises. Those with good wound healing, no hip pain, sound mind, good appetite, no serious complications, and no serious abnormalities in various laboratory indexes were discharged.

The research group adopted a new treatment model, perioperative MDT diagnosis and treatment + individualized surgical plan + risk prediction. Details of the treatment methods are described as follows: (1) After admission, an MDT team, which was led by orthopedic surgeons and composed of professional backbones with intermediate titles or above in geriatrics, critical medicine, anesthesiology, mental health, rehabilitation medicine, and other related departments, was set up. The MDT team evaluated the patients' specific conditions, formulated personalized examination and treatment plans, and opened green channels to shorten the waiting time for examinations. In addition, the mental state of the patients was adjusted to actively prepare them for surgery, and the time between admission and operation was shortened as much as possible; (2) A surgical protocol was jointly developed based on each patient's treatment and fracture type, as assessed by the MDT team. If the hemoglobin count was > 90 g/L after blood transfusion, with no hypertension, lower limb deep venous thrombosis (except for those undergoing inferior vena cava filter placement), preoperative delirium, and serious basic diseases, the internal fixation scheme was determined according to the fracture type. For those with preoperative hypoproteinemia, moderate-to-severe anemia that cannot be corrected, severe underlying diseases, and delirium, among others, the internal fixation method was comprehensively considered in combination with the fracture type, and proximal femoral locking plate (PFLP) fixation was performed when necessary; and (3) During the perioperative period, patients were assessed using the Mini-Cog and orthopedic POSSUM scales for delirium and risk prediction, respectively. Patients who were not eligible for surgery at the time were treated by relevant specialists and re-evaluated after their condition improved. The post-surgical patients were re-evaluated by the MDT team, and timely and effective treatment was given if necessary. Those with multiple medical diseases and more serious conditions were admitted to the intensive care unit after the operation. In addition, mental health practitioners assessed the patients' mental state before and after surgery to better guide the treatment. Moreover, rehabilitation physicians instructed patients to exercise to improve muscle strength and joint range of motion and assisted with early ambulation. Other routine diagnoses, treatments, and discharge standards after the operation were the same as in the control group.

Detection indicators

Hip function: Patients' hip function was assessed using the Harris Hip Score (HHS) before and 6 mo after surgery for pain (0-44 points), function (0-47 points), deformity (0-4 points), and range of motion (0-5 points) components, with a total score of 100 points. A higher score indicated a better hip functional recovery.

Preoperative risk assessment: The orthopedic POSSUM scoring system, which consists of 12 variables forming the physiological assessment (score range 12-96) and 6 variables forming the operative severity assessment (score range 6-48), was used to evaluate the surgical risk of patients. A higher score suggested a greater risk.

Cognitive function assessment: Using the Montreal Cognitive Assessment Scale (MoCA; score range 0-30), the patients' cognitive function (CF) was assessed from 11 items in 8 knowledge fields (memory, language, attention and concentration, executive functions, visuospatial skills, abstraction, calculations, and orientation). In addition, the patients'

Table 1 Analysis of comparability of general data between the two groups

Categories	Control group (*n* = 30)	Research group (*n* = 30)	χ^2 value	*P* value
Sex			0.067	0.796
Male	14 (46.67)	15 (50.00)		
Female	16 (53.33)	15 (50.00)		
Age (yr)	63.20 ± 5.32	62.40 ± 6.04	0.544	0.588
Fracture site			0.617	0.432
Left	11 (36.67)	14 (46.67)		
Right	19 (63.33)	16 (53.33)		
Hypertension			0.635	0.426
Yes	17 (56.67)	20 (66.67)		
No	13 (43.33)	10 (33.33)		
Diabetes			0.373	0.542
Yes	8 (26.67)	6 (20.00)		
No	22 (73.33)	24 (80.00)		

intelligence was assessed using the Mini-Cognitive (Mini-Cog) scale (score range 0-5). Scores on both scales were proportional to CF.

Incidence rate of AEs: AEs that occurred during treatment, such as internal fixation failure, infection, nonunion, malunion, and postoperative delirium, were observed and recorded in all patients, and the incidence rate was calculated.

Clinical indicators: Clinical indicators, including operation time (OT), postoperative hospital length of stay (HLOS), ambulation time, and intraoperative blood loss (IBL), were recorded and compared.

Statistical analysis

All statistical analyses were performed using SPSS 20.0. The mean ± SEM was used to describe continuous variables, and the *t*-test was used for comparison between groups. Categorical variables were expressed as percentages, and the χ^2 test was used for intergroup comparison. $P < 0.05$ was considered statistically significant.

RESULTS

General information

A comparative analysis of patient general data, such as sex, age, fracture site, hypertension, and diabetes, showed clinical comparability between both groups ($P > 0.05$; Table 1).

Hip joint function

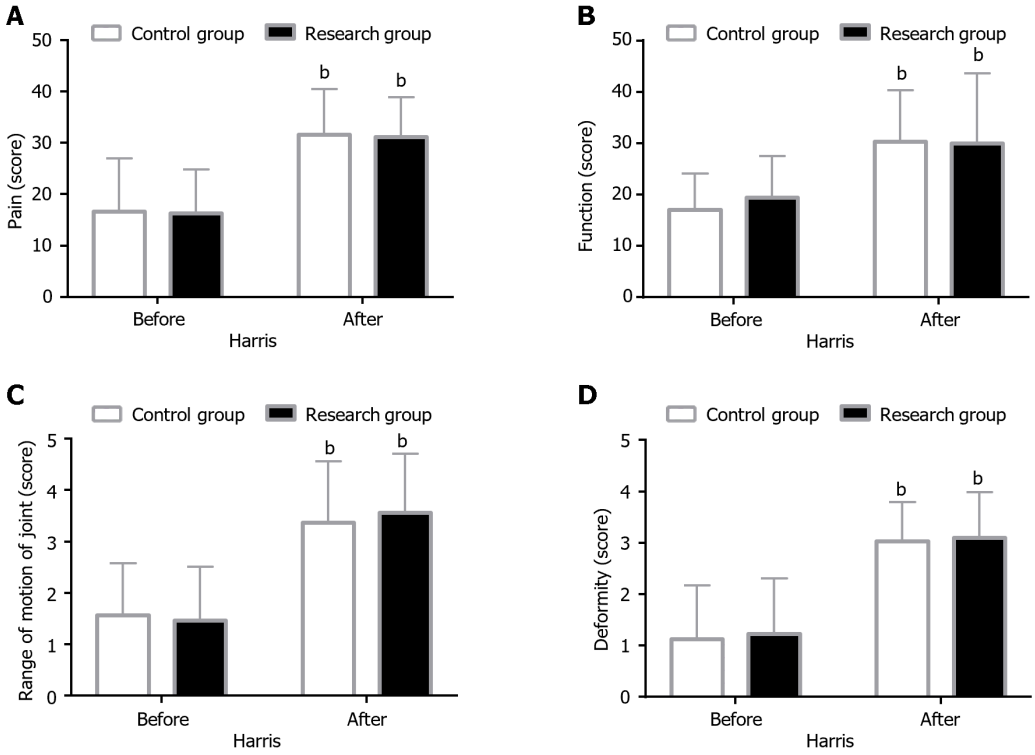
The patients' hip joint function was evaluated by assessing the pain, function, range of motion, and deformity components of the HHS. The analysis showed no significant intergroup difference in HHS scores before and after intervention ($P > 0.05$). However, the intragroup comparison revealed markedly elevated HHS scores in both groups after intervention ($P < 0.05$) (Figure 1).

Orthopedic POSSUM scale scores

After the analysis using the orthopedic POSSUM scale, it was found that the preoperative physiological and operative severity scores of the research group were significantly reduced as compared to the control group ($P < 0.05$) (Figure 2).

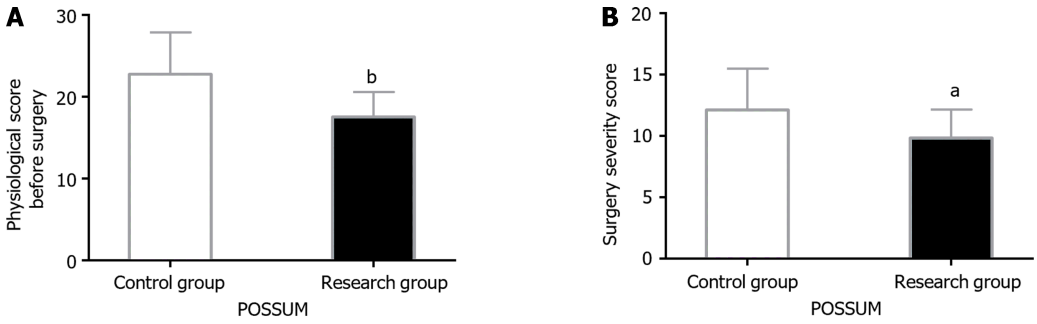
CF

A comparative analysis of patients' CF using the MoCA and Mini-Cog showed no significant difference in both scores between groups prior to the intervention ($P > 0.05$). After the intervention, the MoCA score was significantly reduced in both groups ($P < 0.05$), with an even higher score in the research group ($P < 0.05$). In terms of the Mini-Cog score, a significant decrease was observed in the control group ($P < 0.05$) as opposed to a non-significant decrease in the research group after intervention ($P > 0.05$); however, comparatively, the score remained significantly higher in the research group ($P < 0.05$) (Figure 3).



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Figure 1 Hip function. A: There are no significant differences between the research and control groups in pre- and post-interventional pain scores; however, elevated pain scores relative to the pre-interventional values are observed in both groups; B: There are no significant differences between the two groups in pre- and post-interventional function scores; however, elevated function scores relative to the pre-interventional values are observed in both groups; C: There are no significant differences between the two groups in pre- and post-interventional joint range of motion (ROM) scores; however, elevated joint ROM scores relative to the pre-interventional values are observed in both groups; D: There are no significant differences between the two groups in pre- and post-interventional deformity scores; however, elevated deformity scores relative to the pre-interventional values are observed in both groups. $^{b}P < 0.01$ *vs* before intervention. ROM: Range of motion.



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Figure 2 Orthopedic Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity scale scores. A: Preoperative physiological scores are significantly lower in the research group than in the control group; B: Surgical severity scores are lower in the research group than in the control group. $^{a}P < 0.05$ and $^{b}P < 0.01$ *vs* control group. POSSUM: Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity.

AEs

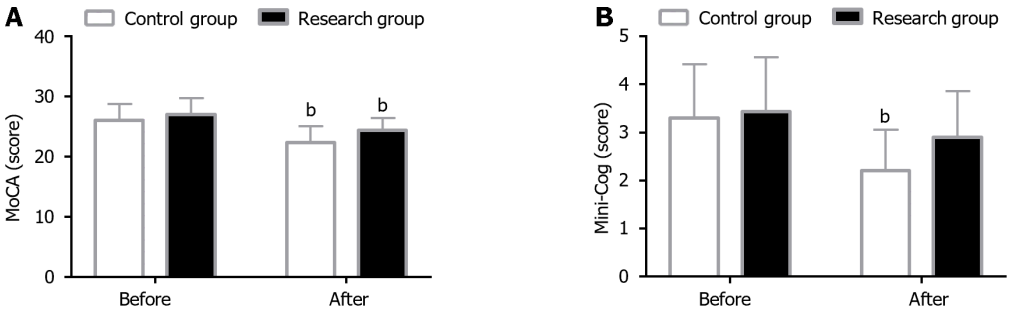
According to the statistics on internal fixation failure, infection, nonunion, malunion, and postoperative delirium, the total incidence of AEs was found to be significantly lower in the research than in the control group ($P < 0.05$; Table 2).

Clinical indexes

The measurement of clinical indexes revealed less OT, postoperative HLOS, and IBL and early ambulation in the research group than in the control group ($P < 0.05$) (Figure 4).

Table 2 Adverse events

Events	Control group (n = 30)	Research group (n = 30)	χ^2 value	P value
Internal fixation failure	1 (3.33)	1 (3.33)	-	-
Infection	2 (6.66)	1 (3.33)	-	-
Nonunion	2 (6.66)	1 (3.33)	-	-
Malunion	2 (6.66)	0 (0.00)	-	-
Postoperative delirium	3 (10.00)	0 (0.00)	-	-
Total	10 (33.33)	3 (10.00)	4.812	0.028



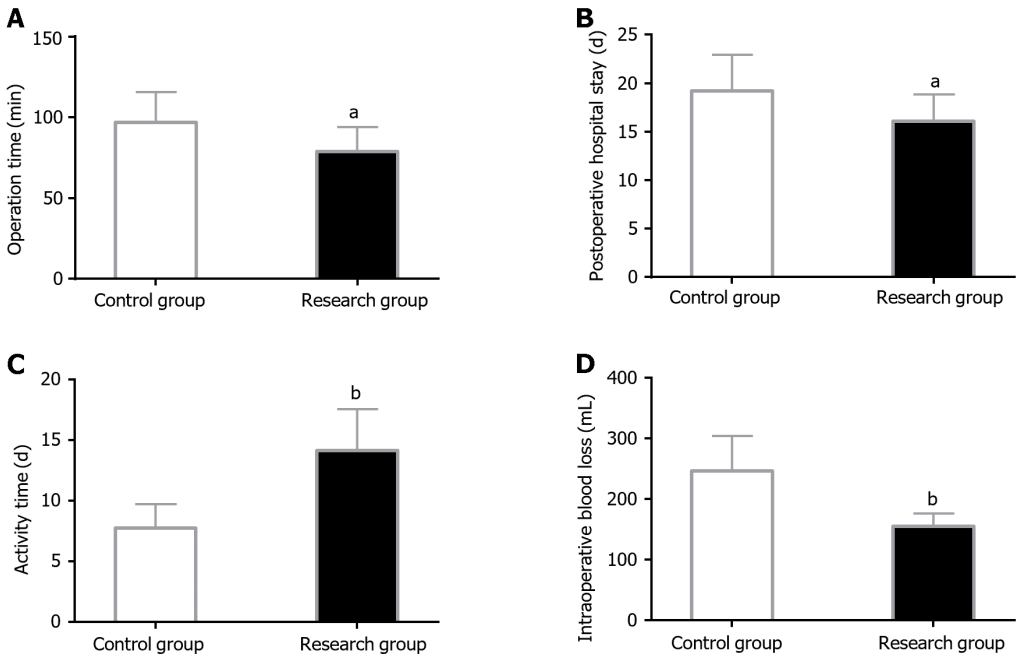
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Figure 3 Cognitive function. A: Montreal cognitive assessment scale scores are markedly reduced in the research group but remained higher than the control group after intervention; B: Mini-Cog scores are slightly altered in the research group but remained higher than in the control group after intervention. $^bP < 0.01$ *vs* before intervention; $P < 0.05$ *vs* control group. MoCA: Montreal cognitive assessment scale; Mini-Cog: Mini-Cognitive.

DISCUSSION

Conventional treatment is less effective in the treatment of elderly patients with EUHFs, and surgery is currently the treatment of choice to help patients regain their independence, including work ability, faster after injury[15]. In addition, the general consultation model adopted in conventional treatment has some shortcomings, such as delayed treatment time due to repeated preoperative consultation and examination, which leads to various complications in some patients waiting for surgery, including loss of the optimal timing for surgery[16]. Given the above problems, developing effective solutions to optimize the diagnosis and treatment experience of elderly patients with EUHF is imperative.

In this study, the new treatment model was based on MDT diagnosis and treatment + individualized surgical plan + risk prediction, with holistic sequential trauma treatment as the concept[17]. However, the conventional treatment model included general consultation + fracture type-guided internal fixation as the main program and local trauma theory as the main guidance[18]. Herein, significantly enhanced hip joint function, reflected in significantly elevated HHS scores in pain, function, range of motion, and deformity dimensions, was observed in both cohorts after surgery. However, no significant intergroup differences were observed, which suggested that the two surgical treatment modalities had similar effects in elderly patients with EUHF. This may be attributed to the guiding exercise for hip functional rehabilitation administered to patients in both treatment protocols. According to Wu *et al*[19], the application of MDT in combination with perioperative management in elderly patients with intertrochanteric fractures not only significantly reduced perioperative symptoms but also effectively facilitated postoperative rehabilitation and long-term improvement of hip function, similar to our findings. Surgical treatment of hip fractures is known to be extremely life-threatening for elderly patients, and the prediction and evaluation of surgical risk based on individual differences can be helpful to improve surgical outcomes[14,20]. Therefore, in this study, we used orthopedic POSSUM and Mini-Cog scales to predict the surgical risk and postoperative delirium in elderly patients with EUHF. The data from the orthopedic POSSUM scale showed that the research group had lower preoperative physiological and operative severity scores than the control group, indicating reduced surgical risk under the intervention of the new treatment model. This may be attributed to the preoperative prediction, accurate assessment, and advanced management of complications in patients under the new treatment model. Previous studies have shown that the POSSUM scale has a certain application value in the risk assessment of hip fracture surgery in elderly patients. Risk management based on this scale, combined with the cooperation of the MDT team, can help reduce the mortality and readmission rates of elderly patients with fractures in the perioperative period and improve their functional outcomes[21,22]. Regarding the MoCA and Mini-Cog scores, the post-interventional scores in the research group were notably higher than the post-interventional values in the control group, indicating that the new treatment model can help prevent postoperative cognitive impairment and delirium in such patients. Postoperative cognitive dysfunction and delirium, which are common postoperative complications in elderly patients with hip fractures, have been associated with a significant increase in postoperative serum S100A12 levels[23,24]. Similarly, Zhu *et al*[25] suggested that perioperative geriatric comprehensive assessment for elderly patients with hip fractures can not



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Figure 4 Clinical indicators. A: Operation time is significantly shorter in the research group than in the control group; B: Postoperative hospital length of stay is significantly shorter in the research group than in the control group; C: Activity time is significantly longer in the research group than in the control group; D: Intraoperative blood loss is statistically less in the research group than in the control group. [a]$P < 0.05$ and [b]$P < 0.01$ *vs* control group.

only shorten the preoperative waiting time and total hospital stay compared with conventional consultation but also reduce the risk of postoperative delirium, in line with our findings.

Among various AEs, the incidence of internal fixation failure, infection, nonunion, malunion, and postoperative delirium was significantly lower in the research than in the control group, suggesting that it is safe for elderly patients with EUHF to receive the new treatment. The aforementioned prevention of postoperative cognitive impairment and delirium helps to avoid prolonged bed rest, subsequently reducing the risk of bedsores and pulmonary infection, including the incidence of postoperative AEs and mortality[26]. In addition, the orthopedic POSSUM scale was introduced in this study for preoperative comprehensive assessment, allowing for causative or symptomatic treatment of the problems found in the evaluation to significantly reduce postoperative AEs, which also explains the above results [27]. Finally, we found that patients in the research group had more clinical advantages than those in the control group in terms of OT, postoperative HLOS, ambulation time, and IBL, suggesting that the new treatment model can shorten treatment time, promote patients' rehabilitation, and improve surgical safety. This may be attributed to the emphasis on local trauma and the neglect of overall trauma in the conventional treatment model, which often leads to long OT, excessive bleeding, and more postoperative complications[28,29]. On the contrary, the new treatment model links the difficulty of anatomical reduction with the operation tolerance time and anesthesia mode and applies traditional PFLP fixation to a small number of patients with poor basic conditions. PFLP fixation, a simple clinical procedure, can not only reduce the interference to the blood supply at the fracture end but also increase the stability and strength of the nail-bone combination, which is conducive to shortening the OT while maintaining a certain therapeutic effect[30]. In a study by Rui *et al*[31], the new treatment model formulated by the MDT team for hip fractures in the elderly is beneficial to shorten the OT and postoperative HLOS, in line with our findings.

CONCLUSION

The new treatment model using MDT diagnosis and treatment + individualized surgical plan + risk prediction was superior to the conventional treatment model of general consultation + fracture type-guided internal fixation in clinical efficacy to a certain extent. The main clinical advantages of the novel treatment model were lower surgical risks, lower incidence of postoperative AEs, more effectively accelerated patient recovery, and prevention against postoperative cognitive dysfunction and delirium, which can improve the treatment efficacy and experience of elderly patients with EUHF and provide more accurate evidence to guide clinical application.

ARTICLE HIGHLIGHTS

Research background

Given the current high perioperative risk of extremely unstable hip fractures (EUHFs) in elderly patients and the unsatisfactory treatment outcomes, there is an urgent need to propose new treatment strategies to treat these patients.

Research motivation

To improve the efficacy and clinical outcome of EUHFs in the elderly, it is necessary to explore and optimize the relevant treatment strategies.

Research objectives

This study focuses on the clinical application effects of two surgical treatment modalities in older adults with EUHFs.

Research methods

First, 60 older adults consecutively diagnosed as EUHFs between September 2020 and January 2022 in the Chongqing University Three Gorges Hospital were selected as the research participants, among which 30 cases in the control group (Con) received conventional treatment (general consultation + fracture type-guided internal fixation) and the other 30 cases in the research group (Res) received novel treatment [perioperative multi-disciplinary treatment (MDT) diagnosis and treatment + individualized surgical plan + risk prediction]. Information on hip function (Harris hip score, HHS), perioperative risk of orthopedic surgery (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity, POSSUM), CF (Montreal cognitive assessment scale, MoCA), postoperative delirium (mini-cognitive, Mini-Cog), AEs (internal fixation failure, infection, nonunion, malunion, and postoperative delirium), clinical indicators (OT; postoperative hospital length of stay, HLOS; ambulation time; intraoperative blood loss, IBL) were collected from both groups for comparative analyses.

Research results

The HHS scores were similar between both groups. The POSSUM score at 6 mo after surgery was significantly lower in the research group compared with the control group, and MoCA and Mini-Cog scores were statistically higher. In addition, the overall postoperative complication rate was significantly lower in the research than in the control group, including reduced OT, postoperative HLOS, ambulation time, and IBL.

Research conclusions

With comparable efficacy in fracture healing, the new treatment modality has some clinical advantages over the conventional treatment, such as less IBL, faster functional recovery, more effectively optimized perioperative quality control, improved postoperative cognitive function, mitigated postoperative delirium, and reduced operation-related adverse events.

Research perspectives

The novel treatment model of MDT diagnosis and treatment + individualized surgical plan + risk prediction can improve the therapeutic efficacy and experience of elderly patients with EUHFs, providing more accurate evidence to guide the management of EUHFs in clinical practice.

FOOTNOTES

Author contributions: Zhou X and Wang HM contributed to the research design and thesis writing; Zhou X, Chen XH, and Li SH collected and analyzed the data; Zhou X, Li N and Liu F contributed to the data collection; Zhou X and Wang HM overall supervise the study; and all authors contributed to the article and approved the submitted version.

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ORIGINAL ARTICLE

Retrospective Study

Nursing model of midwifery and postural and psychological interventions: Impact on maternal and fetal outcomes and negative emotions of primiparas

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Abstract

BACKGROUND

Primiparas are usually at high risk of experiencing perinatal depression, which may cause prolonged labor, increased blood loss, and intensified pain, affecting maternal and fetal outcomes. Therefore, interventions are necessary to improve maternal and fetal outcomes and alleviate primiparas' negative emotions (NEs).

AIM

To discusses the impact of nursing responsibility in midwifery and postural and psychological interventions on maternal and fetal outcomes as well as primiparas' NEs.

METHODS

As participants, 115 primiparas admitted to Quanzhou Maternity and Child Healthcare Hospital between May 2020 and May 2022 were selected. Among them, 56 primiparas (control group, Con) were subjected to conventional midwifery and routine nursing. The remaining 59 (research group, Res) were subjected to the nursing model of midwifery and postural and psychological interventions. Both groups were comparatively analyzed from the perspectives of delivery mode (cesarean, natural, or forceps-assisted), maternal and fetal outcomes (uterine inertia, postpartum hemorrhage, placental abruption, neonatal pulmonary injury, and neonatal asphyxia), NEs (Hamilton Anxiety/Depression-rating Scale, HAMA/HAMD), labor duration, and nursing satisfaction.

RESULTS
The Res exhibited a markedly higher natural delivery rate and nursing satisfaction than the Con. Additionally, the Res indicated a lower incidence of adverse events (*e.g.*, uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia) and shortened duration of various stages of labor. It also showed statistically lower post-interventional HAMA and HAMD scores than the Con and pre-interventional values.

CONCLUSION
The nursing model of midwifery and postural and psychological interventions increase the natural delivery rate and reduce the duration of each labor stage. These are also conducive to improving maternal and fetal outcomes and mitigating primiparas' NEs and thus deserve popularity in clinical practice.

Key Words: Nursing model of midwifery; Postural intervention; Primipara; Maternal and fetal outcomes; Negative emotions

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Core Tip: Primiparas are at high risk for depression during the perinatal period, which can lead to prolonged labor, increased blood loss, and intensified pain that can affect maternal and fetal outcomes. Therefore, it is necessary to give relevant interventions to improve maternal and fetal outcomes and alleviate negative emotions in primiparas.

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INTRODUCTION

Primiparas and multiparas are often at a high risk of experiencing perinatal depression because of the significant physical and psychological burdens they encounter[1]. As reported, the incidence of depression is higher among primiparas than multiparas[2,3]. Clinically, primiparas often develop negative emotions (NEs), such as fear and anxiety, due to severe labor pain caused by inexperience during delivery[4]. Owing to this, mothers may suffer from a lack of strength or improper exertion, leading to prolonged labor, increased blood loss, and intensified pain[5,6]. The type of delivery can also affect maternal and fetal outcomes, with mothers undergoing cesarean section (CS) facing a higher risk of complications[7]. Thus, this study intends to mitigate the NEs of primiparas and improve maternal and fetal outcomes by combining the appropriate nursing model with certain interventions. This study also contributes toward the prevention of maternal complications as well as management optimization during clinical application.

Although routine midwifery and nursing aid primiparas, the quality across medical institutions may vary[8]. There is a need to improve the regulatory effect of routine nursing on maternal NEs[9]. Therefore, our research team adopted the care model of midwifery, a novel model of midwifery nurse practice that prioritizes the psychological and emotional state of mothers and is more humanized[10,11]. In the study on maternal care by Beecher *et al*[12], the improvement of maternal psychological quality under the midwifery responsibility system was demonstrated and its positive effect was affirmed. Besides, Wu *et al*[13] reported on the intervention of primary maternal care, pointing out that combining postural and breathing training under the original nursing model can effectively smoothen the delivery process and improve the outcomes of primiparas.

Currently, there are insufficient studies on the clinical application of the care model of midwifery as well as postural and psychological interventions in primipara nursing management, which is this study's focus. It explores and analyzes the same from the perspectives of delivery mode, maternal and fetal outcomes, NEs, labor duration, and nursing satisfaction. Its ultimate goal is to provide an effective clinical basis for the nursing management of primiparas and improve their delivery experience.

MATERIALS AND METHODS

Study participants

The study participants were 115 primiparas who visited the Quanzhou Maternity and Child Healthcare Hospital between May 2020 and May 2022. The control group (Con; n = 56) was subjected to conventional midwifery and routine nursing; the research group (Res; n = 59) was subjected to the nursing model of midwifery and postural and psychological interventions. Both groups had similar baseline (P > 0.05) and clinical comparability. The inclusion criteria were as follows: Primiparas with full-term pregnancy and normal pelvic diameter after measurement; single pregnancy, normal

fetal presentation, and priority for a vaginal birth; no high-risk maternal complications during pregnancy or pregnancy complications; and normal mental state and verbal communication ability. The exclusion criteria were as follows: Malignancies or organ dysfunction; conditions like nuchal cord, premature rupture of membranes, and amniotic fluid volume abnormality; history of uterine surgery; premature birth or post-term pregnancy; abnormal coagulation function; and autoimmune deficiency.

Methods

The Con was subjected to conventional midwifery and routine nursing. After admission, the midwives on duty provided services, such as routine fetal heart monitoring, maternal skin cleaning, labor process observation, and health guidance. There was no postural intervention during the labor period. The parturient was allowed to choose a comfortable posture, and the midwife delivered the baby after the cervix was fully dilated. Routine nursing measures were also provided.

The Res was subjected to the nursing model of midwifery and postural and psychological interventions. First, one-to-one nursing was provided to each primipara, and a private midwife was there to provide care and management throughout the process of labor preparation and delivery. This not only promoted mutual communication but also facilitated the collection of the primipara's information and the formulation and implementation of nursing strategies, thus improving the efficiency and experience of nursing. The main nursing and management provided by midwives included the following aspects: (1) Prenatal education: Midwives introduced perinatal knowledge to the parturients and informed them of the symptoms they may encounter during the perinatal period and the physiological process of delivery. Through videos and clinical demonstrations, mothers were instructed on pain relief in the first stage of labor through deep breathing, and proper force exertion in the second stage of labor to shorten the labor duration. Additionally, exchanges between multiparas and primiparas were arranged to impart childbirth experience to first-time mothers in order to strengthen their confidence; (2) Psychological intervention: By communicating with the parturients, the midwives evaluated the mothers' potential concerns, depression, fear, and other NEs; they encouraged the mothers to express their worries and provided one-on-one psychological counseling based on the mothers' personality traits and educational level. Furthermore, by enumerating the successful childbirth experiences of other parturients, the midwives enhanced the mothers' confidence in childbirth and relieved their unhealthy psychology; (3) Postural intervention: During the first stage of labor, the parturients were guided to take a free position, with their attention diverted. For mothers with half engagement of non-engagement of fetal presenting part, they were suggested to walk while supporting the belly to speed up the delivery. If the uterine orifice opening was 1-2 cm and the fetus was found to be in an occipital posterior position, the mother was instructed to assume the contralateral prone position during pregnancy, depending on the specific fixed position during pregnancy. During the second stage of labor when the fetal head descended slowly, the mother was instructed to squat according to the maternal situation; (4) Nursing during labor: During labor, the midwife paid close attention to the physical and mental condition of the mother and relieved contraction-induced pain by helping her wipe sweat, massaging the lower abdomen, and expressing encouragement. At the same time, the progress of labor was closely observed. In the case of increased maternal blood loss, uterine contraction weakness, prolonged second labor, fetal distress, and other conditions, the doctor was immediately reported to take timely corresponding measures; and (5) Postpartum care: After the fetus was delivered and processed, it was sent to the mother in time to guide and help early suckling. The newborn was observed in the infant room for two hours and was timely sent back to its mother if there was no abnormality. The midwives also closely observed the vital signs, uterine contraction, and mental state of the postpartum women, especially the amount of postpartum vaginal bleeding, and offered timely interventions when necessary.

Outcome measures

(1) Mode of delivery. The delivery modes of both groups, including CS, natural delivery, and forceps-assisted delivery (FAD), were observed and recorded; (2) Maternal and fetal outcomes. The maternal and fetal outcomes were compared, including uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia; (3) NEs. Maternal NEs were evaluated using the Hamilton Anxiety/Depression-rating Scale (HAMA/HAMD)[14]. HAMA has 14 assessment items, and HAMD has 24 assessment items; each item of both is graded from 0 to 4, with higher scores indicating more serious anxiety or depression symptoms; (4) Duration of labor. The duration of each stage of labor was recorded for comparative analysis; and (5) Nursing satisfaction. Patients were asked to fill in the self-made nursing satisfaction questionnaire of our hospital (0-100 points) to understand their satisfaction with the nursing services. Higher scores are indicative of better satisfaction, with a score of > 80 points, 60-80 points, and < 60 points representing satisfactory, basically satisfactory, and unsatisfactory, respectively.

Statistical processing and analysis

The number of cases/percentage (n, %) and the mean ± SEM were used to represent categorical and continuous variables, respectively. Among these, the χ^2 test was used to compare categorical data, and the independent sample t-test compared the continuous variables between the groups. In this study, the SPSS18.0 software package was used for statistical analysis, and a minimum significance level of $P < 0.05$ was used throughout.

RESULTS

General data of both groups

Both study groups were comparable in terms of age, gestational age, body mass index, smoking history, drinking history, educational level, and other general data ($P > 0.05$) (Table 1).

Delivery modes in both groups

According to the comparative analysis of the delivery modes (CS, natural delivery, and FAD), the Res had a higher natural delivery rate ($P < 0.05$), a lower CS rate ($P < 0.05$), and a comparable FAD rate than the Con ($P > 0.05$) (Table 2).

Maternal and fetal outcomes in both groups

Evaluating and comparing the maternal and fetal outcomes, such as uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia indicated that the incidence of adverse maternal and fetal outcomes described above was statistically lower in the Res ($P < 0.05$) (Table 3).

NEs of both groups

The assessment of maternal anxiety and depression using the HAMA and HAMD revealed that both scale scores were similar in the two groups before the interventions, but they significantly declined after corresponding interventions ($P < 0.05$), with even lower scores in the Res compared to the Con ($P < 0.05$) (Figure 1).

Labor duration in both groups

The time spent in the first, second, and third stages of labor was markedly shorter in the Res than the Con ($P < 0.05$) (Figure 2).

Patient satisfaction with nursing in both groups

Patient satisfaction with the care services was assessed using a self-developed nursing satisfaction questionnaire. The satisfaction of the Res was statistically higher compared to the Con (96.61% *vs* 82.14%, $P < 0.05$) (Table 4).

DISCUSSION

Labor is a physiological process a mother undergoes to deliver an infant, which is accompanied by pain and pressure [15]. Providing scientific and reasonable care management for primiparas is therefore of great value to improve their birthing experience and delivery outcomes. The mode of delivery affects not only maternal and infant health, but also the success rate of breastfeeding[16]. Specifically, although CS is devoid of childbirth pain, it is riskier for maternal and infant health compared to normal delivery; it is associated with a higher risk of maternal mortality and postoperative complications[17,18]. The analysis of delivery modes in this study revealed that the Res had a markedly higher natural delivery rate, a lower CS rate, and a comparable FAD rate than the Con, suggesting that the adoption of the nursing model of midwifery along with postural and psychological interventions can significantly improve the natural delivery rate in primiparas. This may be attributed to the postural guidance provided to the Res, which reduced the oppression of the uterus and the friction caused by the rotation of the carcass, thus ensuring natural delivery[19]. Furthermore, the statistics of maternal and fetal outcomes showed that the incidence of adverse events, such as uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, and neonatal asphyxia, was markedly lower in the Res than in the Con. Thus, the nursing model of midwifery along with postural and psychological interventions is conducive to reducing adverse maternal and fetal outcomes. Considering the potential occurrence of the aforementioned adverse events, this novel nursing model pays close attention to these events and entails timely treatment of such conditions throughout the labor process and postpartum care; this explains the low incidence of adverse events in the Res[20]. In the research of Zhang *et al*[21], continuous midwifery services, which also integrate health education, psychological interventions, and labor and postpartum care, not only elevate the natural delivery rate of primiparas but also significantly improve maternal and fetal outcomes, similar to our findings.

Primiparas are prone to anxiety, fear, and other NEs due to their lack of experience in childbirth; this can affect the progress of labor and the smooth delivery, making psychological interventions crucial[22]. In this study, the Res showed lower HAMA and HAMD scores than the Con after the interventions, indicating that the nursing model of midwifery along with postural and psychological interventions can significantly relieve anxiety, depression, and other NEs in primiparas. This may be related to the fact that the nursing model experienced by the Res included psychological interventions and the timely channelization of maternal NEs[23]. In terms of the labor process, the Con spent more time in the first, second, and third stages of labor than the Res, indicating that the labor process of primiparas is smoother when the nursing model of midwifery and postural and psychological interventions are adopted. In this study, the prenatal education in the nursing management model used in the Res provided primiparas with guidance on the possible problems and coping approaches during the labor process, which helps accelerate the progress of labor[24,25]. Finally, the evaluation of the nursing satisfaction questionnaire showed a satisfaction degree as high as 96.61% in the Res, demonstrating that the nursing model along with the interventions is more popular among first-time mothers and advantageous over the conventional model in clinical practice. Based on the one-to-one nursing model, this novel nursing model provides services, such as prenatal education, psychological and postural interventions, labor care, and

Table 1 General data of both groups of primiparas

Factors	Control group (*n* = 56)	Research group (*n* = 59)	χ^2/t	*P* value
Age (years)	26.80 ± 7.23	28.46 ± 7.20	1.233	0.220
Gestational age (weeks)	37.71 ± 1.58	37.90 ± 1.77	0.606	0.546
BMI (kg/m^2)	22.85 ± 2.95	22.70 ± 3.21	0.261	0.795
History of smoking (yes/no)	14/42	11/48	0.682	0.409
History of alcoholism (yes/no)	10/46	16/43	1.408	0.235
Educational level (primary school or junior high school/senior high school/junior college and above)	17/26/13	18/30/11	0.403	0.818

BMI: Body mass index.

Table 2 Delivery modes of both groups, *n* (%)

Categories	Control group (*n* = 56)	Research group (*n* = 59)	χ^2 value	*P* value
Cesarean section	28 (50.00)	4 (6.78)	26.723	< 0.001
Natural delivery	24 (42.86)	53 (89.83)	28.653	< 0.001
Forceps-assisted delivery	4 (7.14)	2 (3.39)	0.818	0.366

Table 3 Maternal and fetal outcomes of both groups, *n* (%)

Categories	Control group (*n* = 56)	Research group (*n* = 59)	χ^2 value	*P* value
Uterine inertia	17 (30.36)	7 (11.86)	5.950	0.015
Postpartum hemorrhage	6 (10.71)	1 (1.69)	4.089	0.043
Placental abruption	5 (8.93)	0 (0.00)	5.507	0.019
Neonatal lung injury	6 (10.71)	1 (1.69)	4.089	0.043
Neonatal asphyxia	4 (7.14)	0 (0.00)	4.366	0.037

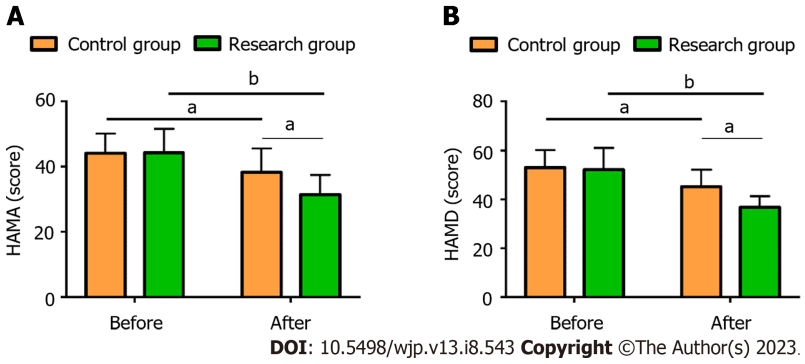
Table 4 Patient satisfaction with nursing in both groups, *n* (%)

Categories	Control group (*n* = 56)	Research group (*n* = 59)	χ^2 value	*P* value
Satisfactory	17 (30.36)	36 (61.02)	-	-
Basically satisfactory	29 (51.79)	21 (35.59)	-	-
Unsatisfactory	10 (17.86)	2 (3.39)	-	-
Satisfaction	46 (82.14)	57 (96.61)	6.434	0.011

postpartum care for primiparas to improve their delivery experience, thus enhancing care quality and nursing satisfaction.

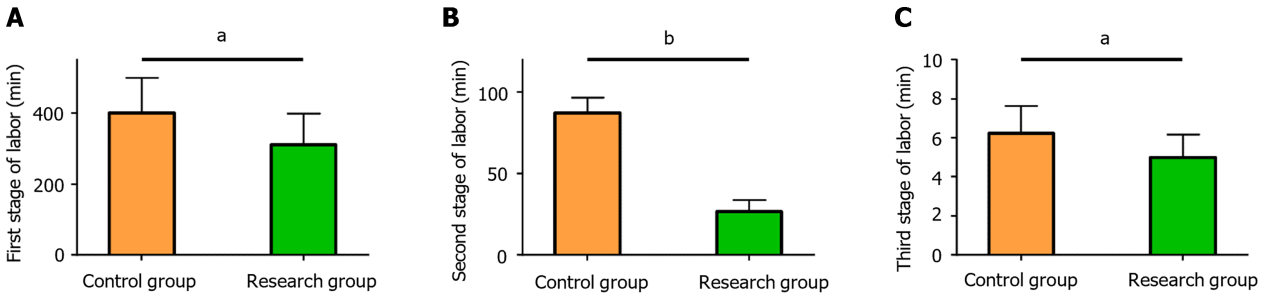
CONCLUSION

For primiparas, the nursing model of midwifery and postural and psychological interventions effectively improves maternal and fetal outcomes. Consequently, maternal anxiety and depression are alleviated, the natural delivery rate and nursing satisfaction increased, and the progress of labor is promoted. Therefore, this technique deserves clinical promotion.



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Figure 1 Hamilton anxiety/depression-rating scale scores. A: Hamilton anxiety before and after intervention; B: Hamilton depression before and after intervention. [a]*P* < 0.05, [b]*P* < 0.01. HAMA: Hamilton anxiety; HAMD: Hamilton depression.



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Figure 2 Duration of each stage of labor. A: Duration of the first stage of labor in both groups; B: Duration of the second stage of labor in both groups; C: Duration of the third stage of labor in both groups. [a]*P* < 0.05, [b]*P* < 0.01.

ARTICLE HIGHLIGHTS

Research background

Parturients are physically and psychologically burdened during the perinatal period, so both primiparas and multiparas are at higher risk of depression. In addition, the mode of delivery of primiparas has an impact on maternal and infant outcomes, and those given birth by cesarean section (CS) are at a higher risk of complications.

Research motivation

To increase people's awareness of perinatal maternal management and provide reference for clinical care optimization of parturients during the perinatal period.

Research objectives

This study aims to analyze the effects of midwifery responsibility nursing plus postural interventions on maternal and fetal outcomes and negative emotions (NEs) of primiparas.

Research methods

In this study, 59 primiparas in the research group were treated by midwifery responsibility nursing plus posture interventions, and 56 primiparas in the control group were given conventional midwifery and routine nursing. The two groups were comparatively analyzed in terms of the mode of delivery, maternal and infant outcomes, NEs (Hamilton Anxiety/Depression-rating Scale, HAMA/HAMD), duration of labor, and nursing satisfaction.

Research results

Significantly higher natural delivery rate and nursing satisfaction, as well markedly lower CS and forceps delivery rates were determined in the research group compared with the control group; the research group also showed obviously lower incidence of uterine inertia, postpartum hemorrhage, placental abruption, neonatal lung injury, neonatal asphyxia and other events and shorter duration of each stage of labor than the control group; moreover, the HAMA and HAMD scores of the research group after intervention were significantly lower than those before treatment and in the control group.

Research conclusions

Midwifery responsibility nursing plus postural interventions is beneficial to improve maternal and infant outcomes, relieve maternal NEs, increase the rate of spontaneous labor, and shorten the duration of natural labor.

Research perspectives

This study mainly analyzes the application value of midwifery responsibility nursing plus postural intervention program in the care management of primiparas, focusing on the exploration and analysis of maternal and infant outcomes and NEs, in an attempt to provide an effective clinical basis for the care management of primiparas and contribute to improving their childbirth experience.

FOOTNOTES

Author contributions: Gao P contributed to the study conception and design, drafting manuscript, data analysis and interpretation; Gao P, Zhuang HP and Guo CQ contributed to the study conception, critical revision of article for important intellectual content; Gao P and Chen MY contributed to the study conception and design, critical revision of article for important intellectual content.

Institutional review board statement: The study was reviewed and approved by the Quanzhou Maternity and Child Healthcare Hospital Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no competing interests.

Data sharing statement: No additional data are available.

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Randomized control trial of a culturally adapted behavioral activation therapy for Muslim patients with depression in Pakistan

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Abstract

BACKGROUND

Behavioral activation therapy (BA) is as effective as cognitive behavior therapy (CBT) in treating depression and can be delivered by practitioners with much less psychological training, making it particularly suitable for low resource settings. BA that is culturally adapted for Muslims (BA-M) is a culturally adapted form of BA that has been found acceptable and feasible for Muslims with depression in the United Kingdom and Turkey; however, this is the first time that its efficacy has been determined through a definitive randomized controlled trial.

AIM

To compare the effectiveness of BA-M with CBT for Muslim patients with depression in Pakistan.

METHODS

One hundred and eight patients were randomized 1:1 to treatment arms in a parallel-group randomized controlled trial in hospital or community sites in Lahore, Pakistan. Recruitment followed self-referral or referrals from clinicians, consultants or relevant professionals at each site. Four measures were recorded by blinded assessors: The patient health questionnaire-9 (PHQ-9); the BA for depression scale short form (BADS-SF); symptom checklist-revised and the World Health Organization Quality-of-Life Brief Scale. All measures were recorded at baseline and post treatment; PHQ-9 and BADS-SF were also recorded at each session and at three month follow up. The primary analysis was to regress the PHQ-9 score after therapy upon the PHQ-9 score before therapy (baseline) and the type of therapy given, that is, analysis of covariance. In addition, analysis using PHQ-9 scores collected at each therapy session was employed in a 2-level regression model.

RESULTS
Patients in the BA-M arm experienced greater improvement in PHQ-9 score of 1.95 units compared to the CBT arm after adjusting for baseline values (P = 0.006) The key reason behind this improvement was that patients were retained in therapy longer under BA-M, in which patients were retained for an average 0.75 sessions more than CBT patients (P = 0.013). Patients also showed significant differences on physical (P < 0.001), psychological (P = 0.004) and social (P = 0.047) domains of Quality of Life (QoL) at post treatment level, indicating an increased QoL in the BA-M group as compared to the treatment as usual group. Some baseline differences were noted in both groups for BA scores and two domains of QoL scale: Physical and environment, which might have influenced the results, though the BA-M group showed more improvement at completion of therapy.

CONCLUSION
Results proved the efficacy of BA-M in reducing symptoms for depressed patients in Pakistan, indicating BA-M is a promising treatment modality for depression in future, particularly in low resource settings.

Key Words: Culturally adapted therapy; Behavioral activation; Depression; Pakistan; Muslim; Randomized control trial

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Core Tip: Behavioral activation therapy that is culturally adapted for Muslims (BA-M) is a more effective treatment for depression in comparison to cognitive behavior therapy (CBT) for Muslim populations within the Pakistani cultural context. Increased engagement with the therapy appears to be the key reason for the significantly lower depression scores of patients receiving BA-M. As this treatment can be delivered by practitioners with much less psychological training than CBT, it is particularly suitable for Muslim patients in low resource settings.

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INTRODUCTION

Depression is a mood disorder with widespread occurrence throughout the world[1,2], affecting more than 300 million people around the globe according to World Health Organization (WHO) estimates. It is ranked as the largest cause of disability worldwide, with more than 4% global prevalence and an upward trend in developing countries, with almost half of cases occurring in South-East Asia[3]. In Pakistan, the risk of developing depression is 10%-25% higher for women than for men and this can be further increased by infertility[4], having a disabled child, emotional setbacks or family issues and disputes[5]. Depression can have a strong impact on family members as well as on the individual with depression[6]. Recorded rates of prevalence for maternal depression in Pakistan are among the highest globally at 28%–36%[7,8] and children of depressed mothers in this context are at an increased risk of being underweight, having poor health with more frequent episodes of diarrhea compared to the children of non-depressed mothers[8,9]. A strong relationship between infertility and psychological comorbidities has also been found[10] and evidence suggests that poverty is strongly linked with depression with almost 50% of low income mothers likely to be depressed[11]. This evidence highlights the need for a cost-effective treatment for depression in Pakistan. Interventions are needed to increase access to treatment and reduce the personal as well as social costs of depression, including impact on daily life, upbringing of children and loss in productivity, such as time taken off from work[12].

Despite the availability of a number of evidence-based therapies for depression, such as cognitive behavioral therapy (CBT), behavioral activation (BA), acceptance and commitment therapy (ACT) and exposure-based therapy[13-15], there is a growing body of empirical evidence about the need for, and effectiveness of, culturally adapted and religion-sensitive therapies[16]. Literature in this area shows that interventions that focus on culture and faith can effectively reduce depression and improve quality of life (QoL)[17,18]. Sensitivity to religious beliefs as a resource for health has been integrated into therapies such as CBT[17,19,20]; counseling[21,22]; ACT[23]; and trauma related therapies[24]. Integrating religious coping in adapted versions of such therapies has proved as effective as existing treatments and faith-adapted therapies have shown more positive results in the management of depressive symptoms in Muslim clients[25,26].

BA that is culturally adapted for Muslims (BA-M), developed for United Kingdom-based Muslim communities, is a successful faith-sensitive adaptation of an existing psychological treatment[27,28]. BA-M therapy is based on BA, an existing evidence-based psychosocial treatment for depression that focuses on clients' values and links these with behavioral goals[29-31]. Piloting of this adapted version has shown that BA-M was feasible within a United Kingdom healthcare setting and was very positively received by Muslim clients[28]. The inclusion of 'client values' in therapy makes BA a particularly suitable treatment for adaptation to diverse cultural needs and it has been successfully adapted and tailored to multiple cultural contexts across the globe[32-34]. The present research is the first study globally to assess

the efficacy of BA-M through a randomized controlled trial with adult depressed patients. The trial was conducted in Pakistan, a low income setting in which the approach was considered relevant for the majority of the population.

MATERIALS AND METHODS

A three-center two-arm parallel block-randomized controlled trial was conducted to estimate the effectiveness of BA-M to treat depression in Pakistan compared to treatment as usual (TAU) using a 1:1 allocation ratio. Patients were allocated at each center in blocks of two with one being randomized to TAU and the other allocated to treatment by BA-M (BA culturally adapted to Muslim faith). There were no changes to the recruitment procedure or methods during the trial. The trial was registered with ISRCTN. Ethical approval was granted by the Faculty of Medicine and Health Ethics Committee at the University of Leeds and the National Bioethics Committee, Pakistan.

Participants

Patients with depression were recruited from outpatient departments of three targeted data sites in Lahore, Pakistan: Mayo Hospital (Mayo), Punjab Institute of Mental Health (PIMH) and the Centre for Clinical Psychology, University of the Punjab, Lahore (CCP). Recruitment followed self-referral or referrals from clinicians, consultants or relevant professionals at each site. All patients were over 18 years of age.

Assessment measures

An Urdu version of the patient health questionnaire (PHQ-9) was used to screen for depression[35] alongside the symptom checklist-revised (SCL-R) - an indigenous screening tool for which psychometric properties are well established [36]. Patients were invited to take part in the trial if their depression score on PHQ-9 was at least 10 and if they had no comorbid psychological disorders, such as bipolar disorder or schizophrenia, could understand the study measures and could give informed consent.

Intervention

Patients were randomized to receive either TAU, which was CBT at each site, or BA, adapted to meet the needs of Muslims patients (BA-M). TAU comprised of 8 sessions of CBT.

BA-M is a culturally tailored version of BA, an existing evidence-based psychosocial treatment for depression, which is as effective as CBT but requires less practitioner training[37]. BA-M comprises 6–12 sessions of treatment involving a values assessment. Muslim clients who select religion as a personal value during this assessment are offered the choice of using a self-help booklet designed to help their recovery[27]. The booklet draws on Islamic religious teachings to promote therapeutic goals and 'positive religious coping' that supports resilience, hopefulness and self-esteem[38]. Patients were treated in outpatient clinics at the three sites following referrals to clinical psychologists involved in delivering the intervention for the trial.

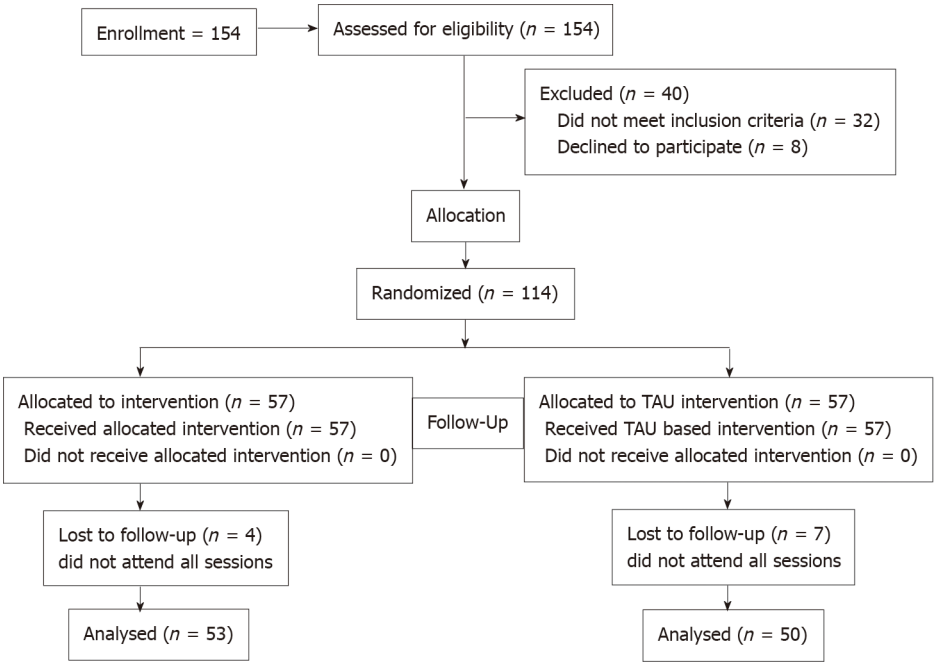
Outcomes

A demographic information sheet with details of age, gender, education, birth order, family income and type, psychological illness, physical illness, current diagnosis and history of treatment related to psychological issues was administered to each recruited patient. The primary outcome, on which the trial was powered, was the change in PHQ-9 score following therapy, that is, the difference between the PHQ-9 score after therapy and that recorded before therapy commenced. The PHQ-9 measure was used to assess depression and determined the extent to which patients had experienced depressive symptoms over the previous two weeks. The nine items were rated on a 0-3 scale ranging from 'not at all' to 'nearly every day'. The PHQ-9 has adequate construct validity and sensitivity to change[39]. In the present study, the Urdu translated version of PHQ-9 was used[7].

There were several secondary outcomes collected to provide greater understanding of the performance of BA-M as a therapy. PHQ-9 was collected not just at baseline and at the end of treatment but at the start of every therapy session. Two other measures were collected before and after therapy. The 9-item BA for depression scale short form (BADS-SF) was used to track activation, including when and how clients became activated during the course of treatment. This measure was developed to improve the original BADS measure and has stronger psychometric properties[40]. The SCL-R [36] is an indigenous checklist which assesses six psychopathologies: Depression, anxiety, obsessive compulsive disorder, somatization, schizophrenia and low frustration tolerance. In the present study, the subscale of depression with 24 items was used to assess the degree of depression in depressed patients. The items are rated on a 4-point Likert scale and psychometric properties are well established for all subscales of SCL-R. A fourth measure, the WHO QoL Brief Scale (WHOQOL-BREF)[41], developed by the WHO with 26 items, was used to assess QoL in depressed patients. This covers 4 major domains: physical health, psychological health, social relationships and environment. One item from each of the 24 facets contained in the WHOQOL-100 was included along with two items from the overall QoL and the general health facets. A further outcome measure was the number of sessions attended by each patient to assess patient engagement with therapy.

Sample size

Power calculations for the sample were based on change in PHQ-9 from baseline (PHQ-9-0) to 3 mo after therapy (PHQ-9-3). Drawing on earlier research, we anticipated that PHQ-9 would have a standard deviation of 5 units and that the



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Figure 1 Flow diagram representing process of the study. TAU: Treatment as usual.

correlation between before and after measurements would be 0.75. Consequently, we anticipated that the difference between PHQ-9-3 and PHQ-9-0 would have a standard deviation of 3.54 units[42]. A minimal clinically important difference in PHQ scores was considered to be 2 units on PHQ-9. Using a two-sample *t*-test to assess the difference between the groups, with 5% significance level, the number required to achieve 80% power is 50 patients per group. It was anticipated that around 15% patients would drop out of the trial before the completion of therapy. Adjusting for drop out thus yielded a sample size of 59 patients per group.

Randomization

At each site, patients were recruited in pairs by a blind assessor who screened for depression and assigned individuals from each pair at random (using a Microsoft Excel random number generator value below 0.5) to TAU or BA-M. This ensured a random sample balanced for each site and for therapy. It was not possible to conceal the randomization from either the patient or those delivering therapy.

Statistical methods

The primary analysis was to regress the PHQ-9 score after therapy upon the PHQ-9 score before therapy (baseline) and the type of therapy given. This analysis of covariance approach was considered to be the optimum statistical method for the analysis of continuous outcomes of randomized control trials (RCTs) where baseline measurements are available[43].

Analysis was undertaken on a complete case basis and the implication for bias due to drop out was considered through analysis of the secondary outcomes. It was not appropriate to assume that data was missing at random since patients may have withdrawn from the trial or from therapy because they were either dissatisfied with their progress through therapy or improved so much that they considered that therapy was no longer required. Hence imputation methods which are valid under the assumption of missing at random were not appropriate here.

As a secondary analysis of PHQ-9, all of the measurements made were considered in a two- level regression analysis with measurements nested within patients by the inclusion of a random intercept for patient. This provided the average change in score per session for each of the two therapies. A Wald test for the interaction term made it possible to formally test if there was a difference in therapy per session.

The average number of sessions attended for each arm was compared with a two-sample *t*-test to explore the duration of the therapy in each arm. Other secondary outcomes, namely BADS-SF, the total SCL-R score, and the four domains of WHOQOL-BREF were compared with analysis of covariance, as for the primary analysis of PHQ-9.

RESULTS

Participant flow

For each group, TAU and BA-M, the numbers of participants who were randomly assigned, received intended treatment and were analyzed for the primary outcome, namely change in PHQ-9 after treatment, is shown in Figure 1.

Table 1 Baseline characteristics of patients stratified by therapy arm

Characteristics		BA-M		TAU		*P* value
		Mean or count	SD or %	Mean or count	SD or %	
Age		32.3	9.6	33.8	11.5	0.437
Gender	Men	17	30%	24	42%	0.242
	Women	40	70%	33	58%	
Data site	CCP	18	34%	22	39%	0.880
	PIMH	21	40%	21	37%	
	Mayo	14	26%	14	25%	
Education	Below primary	6	11%	6	11%	0.300
	Matric	11	20%	14	25%	
	FA/A Level	9	16%	12	21%	
	Other	24	43%	14	25%	
	Middle/secondary	6	11%	11	19%	
Marital status	Married	27	47%	19	33%	0.039
	Sep/divorced/widowed	5	9%	15	26%	
	Unmarried	25	44%	23	40%	
Family system	Nuclear	32	56%	31	54%	0.999
	Joint	25	44%	26	46%	
Working status	Yes	25	45%	21	37%	0.514
	No	31	55%	36	63%	
SES	Lower class	14	25%	21	37%	0.247
	Middle or upper class	42	75%	36	63%	
PHQ (Pre)		19.5	4.9	20.1	4.1	0.487
BADS (Pre)		20.2	8.4	15.6	6.3	0.001
SCL-R (Dep)		41.9	9.9	43.1	8.2	0.506
D1 (Pre)	Physical health	17.9	4.9	14.7	4.8	0.001
D2 (Pre)	Psychological health	12.3	3.3	11.7	3.3	0.333
D3 (Pre)	Social relationships	8.4	2.6	7.9	2.6	0.298
D4 (Pre)	Environment	22.4	5.2	20.0	5.1	0.014

BA-M: Behavioral activation therapy that is culturally adapted for Muslims; TAU: Treatment as usual; CCP: Centre for Clinical Psychology, Lahore; PIMH: Punjab Institute of Mental Health, Lahore; FA/A: Upper secondary level education; PHQ: Patient health questionnaire; BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; D: Domain; Dep: Depression.

Recruitment

The first patient was recruited in March 2020 and recruitment continued until at least 59 patients completed their therapy in each arm. Recruitment was then closed in August 2021, having established that at least 50 patients had been recruited and retained until the end of therapy.

Baseline data

Characteristics between the two groups were similar (Table 1) apart from the initial BADS-SF score and the initial values of the D2 (psychological health) and D4 (environment) domains of WHOQOL-BREF. Analysis methods were designed to adjust for these baseline imbalances.

Drop out

Seven of 57 patients assigned to TAU and 4 of 57 patients assigned to BA-M withdrew from the trial. Data after baseline collection was not available for analysis for these patients. Table 2 shows the characteristics of patients who were lost to follow up compared to those who were retained.

Table 2 Characteristics of lost and retained patients

Characteristics		Lost to follow up (*n* = 11)	Retained (*n* = 103)	*P* value
Age, mean (SD)		35.27 (13.94)	32.83 (10.19)	0.469
Gender	Men	9 (82%)	32 (31%)	0.003
	Women	2 (18%)	71 (69%)	
Education	Below primary	1 (10%)	11 (11%)	
	Matric	3 (30%)	22 (21%)	
	FA/A Level	1 (10%)	20 (19%)	0.915
	Other	3 (30%)	35 (34%)	
	Middle/secondary	2 (20%)	15 (15%)	
Marital status	Married	3 (27%)	43 (42%)	0.617
	Sep/divorced/widowed	2 (18%)	18 (18%)	
	Unmarried	6 (55%)	42 (41%)	
Family system	Nuclear	10 (91%)	53 (52%)	0.029
	Joint	1 (9%)	50 (49%)	
Working status	Yes	5 (46%)	41 (40%)	0.989
	No	6 (55%)	61 (60%)	
SES	Lower class	6 (55%)	29 (28%)	0.151
	Middle or upper class	5 (46%)	73 (72%)	
PHQ Pre		20.18 (2.82)	19.79 (4.71)	0.786
BADS Pre		14.09 (4.11)	18.34 (7.90)	0.082
SCL-R (Dep)		36.91 (9.61)	43.14 (8.88)	0.030
D1 (Pre)	Physical health	16.64 (2.94)	16.33 (5.26)	0.850
D2 (Pre)	Psychological health	12.18 (3.06)	11.94 (3.31)	0.818
D3 (Pre)	Social relationships	8.00 (1.41)	8.17 (2.70)	0.842
D4 (Pre)	Environment	20.18 (3.06)	21.31 (5.44)	0.501

SES: Socioeconomic status; FA/A: Upper secondary level education; PHQ: Patient health questionnaire; BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; D: Domain; Dep: Depression

Male patients and those in nuclear families were seen to be more susceptible to drop out. Feedback from therapists indicated that therapy sessions during working hours were more likely to adversely affect attendance by men and the average baseline SCL-R value was also lower among drop outs, indicating less severe depressive symptoms in this group. Data for 50 TAU patients and 53 BA-M patients was available for analysis.

Outcomes and estimation

A summary of the outcome variables after therapy is provided in Table 3. This provides unadjusted *t*-test comparisons of the outcomes between groups. Significant post treatment differences in depression ($P = 0.006$) and QoL scores were found in the BA group compared to TAU following completion of treatment.

The primary outcome (PHQ-9) was also regressed upon baseline values and therapy arm and the table of regression coefficients is given in Table 4.

From the coefficients in Table 4, it is seen that generally those in the TAU arm have higher PHQ-9 scores after therapy and that an adjustment for baseline values of PHQ-9 is important since the coefficient is statistically significant at the 5% level. Plots of residuals (not shown due to space limitations) were seen as satisfactory. The interpretation for this trial based on the primary analysis is that BA-M is associated with a greater reduction in depression symptoms as measured by PHQ-9 after completion of therapy.

Further analyses

The analysis of secondary outcomes BADS-SF and SCL-R are summarized in Table 5.

Table 3 Summary of outcome after therapy

Characteristics	BA-M	TAU	*P* value
n	57	57	
Drop Out	4 (7%)	7 (12%)	0.526
Retained	53 (93%)	50 (88%)	
PHQ (Post), mean (SD)	4.19 (3.42)	6.18 (3.85)	0.006
BADS (Post)	34.34 (7.32)	27.90 (8.53)	< 0.001
SCL-R (Dep)	16.00 (8.08)	19.96 (7.74)	0.013
D1 Physical Health (Post)	25.85 (2.91)	22.84 (3.35)	< 0.001
D2 Psychological Health (Post)	19.74 (3.08)	17.88 (3.26)	0.004
D3 Social Relationships (Post)	10.45 (1.96)	9.64 (2.15)	0.047
D4 Environment (Post)	27.83 (4.91)	26.48 (4.44)	0.147
Number of Sessions	9.00 (1.77)	8.25 (1.39)	0.013

BA: Behavioral activation therapy; BA-M: Behavioral activation therapy that is culturally adapted for Muslims; TAU: Treatment as usual; PHQ: Patient health questionnaire; BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; D: Domain; Dep: Depression.

Table 4 Coefficients for the regression of the patient health questionnaire-9 post-therapy measurement on baseline and therapy arm

Characteristics	Estimate	95%CI	*P* value
Intercept	1.205	(-1.887, 4.298)	0.441
TAU Arm	1.946	(0.545, 3.347)	0.007
Baseline PHQ	0.152	(0.002, 0.301)	0.046

TAU: Treatment as usual; PHQ: Patient health questionnaire.

As the PHQ-9 tool was used at every therapy session, more detailed longitudinal data was available. Values are plotted in Figure 2.

Figure 2 shows that the PHQ-9 trajectories might be simply modeled with a linear decrease by session. This was undertaken with a linear mixed effects model with a random intercept for patient. The coefficients are shown in Table 6.

The results revealed that the interpretation of the coefficients in Table 6 showed a decline in PHQ-9 of 2.26 points on average for every session attended and there is little evidence of BA-M being superior to TAU on this basis. The reason behind the statistically significant improvement due to BA-M therapy rather than TAU, as seen in the analysis of primary outcome, is that patients under BA-M are retained in therapy longer. Table 3 also shows that the mean number of sessions attended increases from 8.25 under TAU to 9.00 under BA-M ($P = 0.013$).

DISCUSSION

This is the first trial evaluation of the BA-M culturally adapted therapy for depression globally. Previous evaluations have shown feasibility and acceptability to therapists and patients in both United Kingdom[27] and Turkish settings[44]. Findings confirm the importance of culturally adapted approaches when delivering mental health therapies developed in Western contexts to non-Western populations[16] and the benefits of faith-sensitive approaches in general[25]. The results of the current study support the efficacy of BA-M therapy in line with the wider literature on BA as a cost-effective and efficacious alternative to CBT[45]. Patients in the BA-M group showed lower levels of depression (PHQ-9 and SCL-R) and higher scores of BA (BADS-SF) post treatment, indicating the effectiveness of BA-M therapy in reducing depression and increasing helpful activity in patients. Patients also showed significant differences on physical ($P < 0.001$), psychological ($P = 0.004$) and social ($P = 0.047$) domains of QoL at post treatment level, indicating an increased QoL in the BA-M group as compared to the TAU group.

Retention in BA-M therapy

Fewer patients dropped out of the BA-M group than from the TAU group and this was seen to lead to greater benefit since the improvement in symptoms per session was consistent throughout the usual therapy period of 8 wk. Patients who dropped out tended to have low scores on the depression scale as compared to those who were retained. The results

Table 5 Coefficients from the regression for secondary outcomes from analysis of covariance models

Characteristics	Estimate	95%CI	*P* value
BADS			
Intercept	36.332	(31.629, 41.035)	< 0.001
Arm TAU	-6.854	(-10.076, -3.631)	< 0.001
Baseline BADS	-0.098	(-0.302, 0.107)	0.346
SCL-R (Dep)			
Intercept	0.455	(-6.723, 7.633)	0.900
Arm TAU	3.802	(0.960, 6.644)	0.009
Baseline SCL-R (Dep)	-0.098	(-0.302, 0.107)	0.346
WHOQOL (D1: Physical)			
Intercept	22.948	(20.662, 25.235)	< 0.001
Arm TAU	-2.489	(-3.737, -1.241)	< 0.001
Baseline (D1: Physical)	0.162	(0.043, 0.281)	0.008
WHOQOL (D2: Psychological)			
Intercept	16.097	(13.71, 25.235)	< 0.001
Arm TAU	-1.614	(-2.809, -0.420)	0.009
Baseline (D2: Psychological)	0.295	(0.133, 0.476)	0.002
WHOQOL (D3: Social)			
Intercept	7.836	(6.583, 9.089)	< 0.001
Arm TAU	-0.688	(-1.424, 0.048)	0.066
Baseline (D3: Social)	0.313	(0.176, 0.450)	< 0.001
WHOQOL (D4: Environment)			
Intercept	18.072	(14.496, 21.648)	< 0.001
Arm TAU	-0.328	(-1.967, 1.312)	0.693
Baseline (D4: Environment)	0.435	(0.283, 0.586)	< 0.001

BADS: Behavioral activation for depression scale short form; SCL-R: Symptom checklist-revised; WHOQOL: World Health Organization quality of life; D: Domain; Dep: Depression; TAU: Treatment as usual; PHQ: Patient health questionnaire.

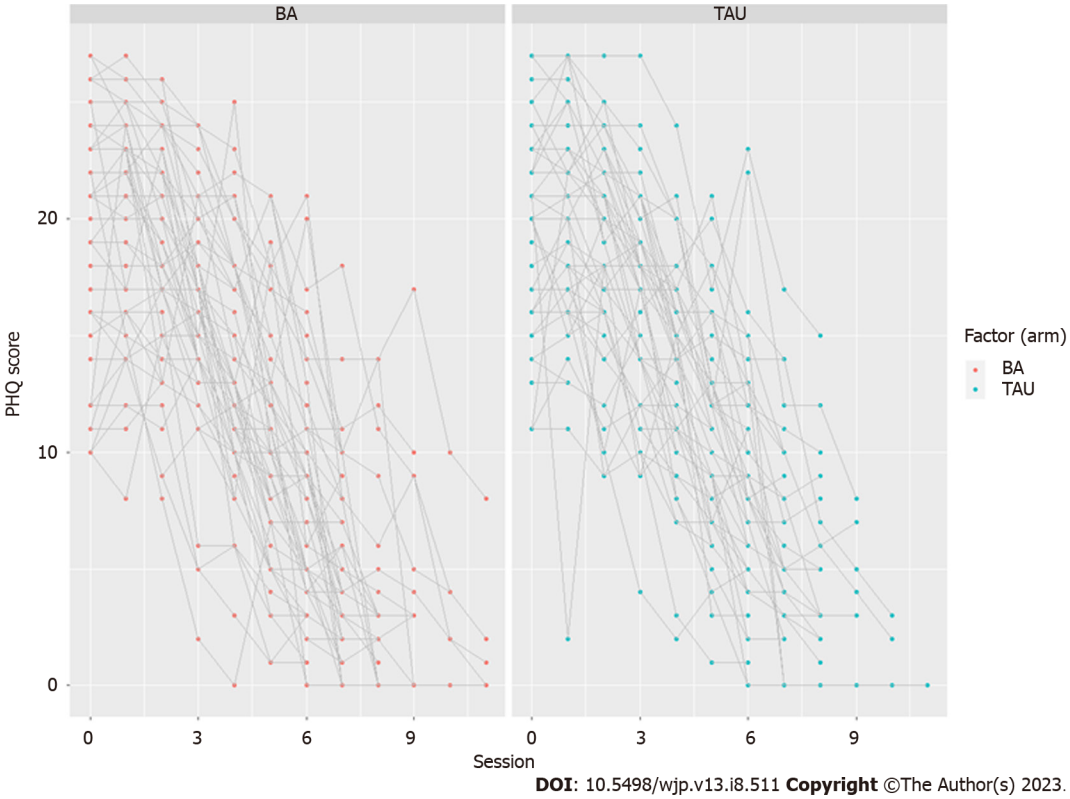
Table 6 Coefficients for the fixed effects of the longitudinal model for patient health questionnaire-9

Characteristics	Estimate	95%CI	*P* value
Overall Intercept	21.536	(20.549, 22.524)	< 0.001
TAU Arm	0.396	(-1.010, 1.800)	0.582
Session	-2.260	(-2.363, -2.156)	< 0.001
TAU-session interaction	0.10203	(-0.058, 0.261)	0.210

TAU: Treatment as usual.

also showed that men and those who were living in nuclear families were found to be more susceptible to drop out.

The particular benefits of BA-M appear to have been achieved as a result of patient retention in therapy and this is an important factor in recovery from depression. As in the United Kingdom study for BA-M[27], the faith-sensitive approach appears to have a motivating influence on patients. Qualitative findings from the United Kingdom study indicated that most patients were enthusiastic about and motivated by the engagement with religious identity in this approach. This was designed to support 'positive religious coping' that increased resilience, hope and self-esteem[38]. The findings confirm previous research, both on value-based practice that takes account of cultural context and on BA, which partic-



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Figure 2 Plot of patient health questionnaire-9 values observed at every therapy session. BA: Behavioral activation therapy; TAU: Treatment as usual; PHQ: Patient health questionnaire.

ularly focuses on increasing activities that are linked to an individual's values and reward systems, consequently enhancing their behavioral patterns and reducing depressive symptoms[46,47].

We note there were important baseline differences in both groups for BA scores and two domains of QoL scale: Physical and Environment. The BA-M group showed more BA and QoL related to physical health and environment as compared to the TAU group. These may have influenced findings although it is clear that there was greater improvement in physical, psychological and social QoL domains for the BA-M group at completion of treatment.

There were also gender differences in retained and dropped out patients as 82% of dropped out patients were men. Differences in the family system of patients were also apparent as 91% of dropped out patients were from nuclear families.

CONCLUSION

In conclusion, this RCT demonstrated the benefit of BA-M, a culturally adapted form of BA, over usual treatment (CBT) at the end of therapy. It is clear that both CBT and BA-M are successful therapies for reducing depression, however, findings suggest that the additional benefit of BA-M is due to greater retention of participants in therapy that is likely to be due to the cultural adaptation. The trial confirms existing evidence on the benefits of therapy that supports activation of religious behaviors as a resource for health and fulfills the need for rigorous research in a population sample that has hitherto been underrepresented and for whom such behaviors may be critical to treatment outcomes[48].

ARTICLE HIGHLIGHTS

Research background

Depression is the largest cause of disability worldwide and can strongly impact on families and society as well as individuals. Culturally appropriate, accessible and cost-effective treatments are needed in low resource settings such as Pakistan. This study is the first randomized control trial globally of behavioral activation (BA) therapy that is culturally adapted for Muslim patients (BA-M).

Research motivation

The main focus was to explore whether BA-M, as a culturally adapted therapy, would achieve better results than

cognitive behavior therapy (CBT), a standard treatment developed in a Western context. BA can be delivered by practitioners with much less psychological training than CBT, making it particularly suitable for low resource settings. This research has great significance for future studies on how to reduce depression and increase access to treatment for Muslim communities worldwide.

Research objectives

The purpose of the study was to compare the effectiveness of BA-M with CBT for Muslim patients in Pakistan.

Research methods

Clinical data were analyzed for 108 patients in a parallel-group randomized controlled trial in hospital or community sites in Lahore, Pakistan. Four measures were recorded by blinded assessors: The patient health questionnaire-9 (PHQ-9); the BA for depression scale short form (BADS-SF); symptom checklist-revised and the WHOQOL-BREF quality of life (QoL) scale. All measures were recorded at baseline and post treatment; PHQ-9 and BADS-SF were also recorded at each session and at three month follow up. The primary analysis was to regress the PHQ-9 score after therapy upon the PHQ-9 score before therapy (baseline) and the type of therapy given. In addition, analysis using PHQ-9 scores collected at each therapy session was employed in a 2-level regression model.

Research results

Patients in the BA-M arm experienced greater improvement in PHQ-9 score compared to the CBT arm and were retained in therapy longer than those receiving CBT after adjusting for baseline values. BA-M patients also showed significant differences on physical, psychological and social domains of QoL at post treatment level, indicating an increased QoL in the BA-M group as compared to the CBT group.

Research conclusions

BA-M is a culturally appropriate treatment for depression that achieves better results than CBT, which is current standard treatment in Pakistan. BA-M can be delivered by practitioners with much less psychological training than CBT and is a promising treatment modality for depression in Muslim communities, particularly in low resource settings.

Research perspectives

Future research should evaluate acceptability and effectiveness of BA-M in other Muslim populations, including where these constitute minorities, and issues related to implementation and scale-up.

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FOOTNOTES

Author contributions: Dawood S was involved in design of the study, led the data collection and conduct of research on data sites, contributed to analysis and drafted the write-up of results; West RM contributed to the trial design, led statistical analysis and contributed to the writing-up of results and final paper; Mir G developed the concept for the study, contributed to the methodology of the randomized control trial and writing of the final paper and gave final approval of the version to be published; All authors contributed and approved the final manuscript.

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Clinical trial registration statement: This study is registered at ISRCTN, No. 35418604.

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ORIGINAL ARTICLE

Observational Study

Effects of sports on school adaptability, resilience and cell phone addiction tendency of high school students

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Abstract

BACKGROUND

Sport help promote healthy physical and mental development of high school students. To date, there have been few studies on the effect of sport on school adaptability, resilience and cell phone addiction tendency of high school students.

AIM

To explore the effects of sports on school adaptability, resilience and cell phone addiction of high school students.

METHODS

A stratified random sampling method was used to select 600 students from two high schools in Lhasa, and Physical Activity Rating Scale, School Adjustment Scale for High School Students, Chinese Adolescents Resilience Scale, and Mobile Phone Addiction Index were used for field questionnaire survey.

RESULTS

Sport was positively correlated with school adaptability and resilience ($P < 0.01$), school adaptability was positively correlated with resilience ($P < 0.01$) and cell phone addiction was negatively correlated with sports, school adaptability and resilience ($P < 0.01$). The direct effect of sport on cell phone addiction was significant ($P < 0.001$), accounting for 20.51% of the total effect. The mediating effect of school adaptability on sport and cell phone addiction was significant ($P < 0.001$), accounting for 17.38% and 35.36% of the total effect value, respectively. School adjustment and resilience had a significant chain-mediated effect on sport and cell phone addiction ($P < 0.001$), accounting for 26.75% of the total effect.

CONCLUSION
Sport affected the cell phone addiction tendency of senior high school students through the mediating effect of school adaptability and resilience, and through the chain mediation effect of both.

Key Words: Sport; High school students; School adaptability; Resilience; Cell phone addiction

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Core Tip: Sport is beneficial to the development of heart and lung function and motor system, and can develop physical strength and promote mental health. This study analyzed the questionnaire data of 560 high school students' sporting activity, school adaptability, resilience and cell phone addiction tendency. By constructing a chain mediation model, the relationship between sport and school adaptability, resilience and cell phone addiction tendency was obtained, providing a theoretical basis for the physical and mental health development of high school students.

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INTRODUCTION

High school students are in a stage of growth and development, and sport plays a particularly important role in promoting their physical and mental health[1]. However, many high school students neglect sport because they study all day under academic pressure or are addicted to their cell phones[2,3]. The decline in sport could have a negative effect on physical and mental health of high school students[4]. Sport can improve high school students' adaptability to school, which can promote interpersonal relations and enthusiasm for learning[5]. Sport can enhance the resilience of high school students, and help them to face the pressure and difficulties brought by school life with a more positive and optimistic attitude[6]. Sport is also linked to lower levels of cell phone addiction among senior high school students[7]. Although many studies have shown that sport has an impact on school adaptability, resilience and cell phone addiction of adolescent students[8-11], few studies have combined sport with these other aspects in high school students. Therefore, by establishing the amount of sport of high school students, we analyzed the relationship between sport and senior high school students' school adaptability, resilience and cell phone addiction tendency. We also discussed the influence of sport on high school students' school adaptability, resilience and cell phone addiction tendency.

MATERIALS AND METHODS

Research object

From March to June 2022, a questionnaire survey was conducted among students from two high schools in Lhasa using stratified random sampling. A total of 600 students were selected according to different grades, and 200 in each grade were selected. The mean age was 16.56 years ± 1.01 years. There were 320 male students (53.33%) with an average age of 16.58 years ± 1.0 years. There were 280 female students (46.67%) with an average age of 16.53 years ± 1.04 years. We included senior grade one, two and three students, and students gave informed consent to complete the questionnaire. We excluded students with poor physical and mental health, and those who were unable to cooperate with the questionnaire. This study is in accordance with the Declaration of Helsinki.

Questionnaire

The questionnaire was conducted with the consent of the students, their parents and the school. Before the test, a mental health professional instructed the students to fill in the questionnaire according to their own situation. After filling in the questionnaire, it was recovered immediately. Six hundred questionnaires were sent out, and 560 (93.33%) were collected.

Research tools

Physical activity rating scale: The Physical Activity scale modified by Liang *et al*[12] was adopted, which measured sport from three dimensions of participation; namely time, intensity and frequency. Score = sport intensity score "(sport time score-1)" sport frequency score. Each dimension was divided into five grades, scoring 1-5 points. Scores ranged from 0 to 100: Low level of sport ≤ 19 points; level 20-42 points, and high level ≥ 43 points. Cronbach's α was 0.82.

School adjustment scale: We used Hou *et al*[13] School Adjustment Scale for Senior High School Students. The scale consisted of 82 items, including seven dimensions of academic adjustment, peer relationship, school attitude, class

activity adjustment, emotional adjustment, conflict in teacher-student relationship, and intimacy of teacher-student relationship. A 5-point Likert 5 scale was used. Scores ranged from 1 to 5. All dimensions were added together to obtain the School Adaptation Score. A higher total score indicated better school adaptability. Cronbach's α was 0.964.

Resilience scale for Chinese adolescents: Hu *et al*[14] compiled the Resilience Scale for Chinese adolescents. The scale consisted of 27 items, including five dimensions: Goal focus, positive cognition, emotional control, family support, and interpersonal assistance. The scale used a 5-point Likert scoring method. Scores ranged from 1 to 5, and a higher total score indicated greater resilience. Cronbach's α was 0.86.

Mobile phone addiction index: The Mobile Phone Addiction Index was compiled by Leung[15]. There were 17 items, including four dimensions: Loss of control, withdrawal, inefficiency and escape. A 5-point Likert scoring method was used. Scores ranged from 1 to 5, and a score < 34 was considered to show no cell phone addiction, 34-51 mild addiction, 52-68 addiction, and 68-85 severe addiction. Cronbach's α was 0.90.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Descriptive statistics, *t* test, analysis of variance, and correlation analysis were conducted on the collected data, and PROCESS was used to test the mediating effect. The statistical significance was $P < 0.05$.

RESULTS

Essential features of senior high school sport

The total score for level of sport in high school students was 16 (6, 30) points (Table 1). The level of sport of high school students was mostly in the low sport level, accounting for 59.29% of the total number.

The level of sport among high school students was significantly higher in male than female students ($P < 0.05$) (Table 2). Sport intensity, time and frequency and total score were also significantly higher in male students ($P < 0.05$), indicating that male students had a greater need of sport.

There were no significant differences in sport intensity, time and frequency in senior grade one, two and three students ($P > 0.05$) (Figure 1).

Among the 560 high school students participating in the survey 332 (59.29%) had a low level of sport, 144 (25.71%) had a medium level, and 84 (15%) had a high level (Table 1). Among the 300 male students, 157 (52.33%) had a low level of sport, 82 (27.33%) had a medium level, and 61 (20.34%) had a high level. Among the 260 female students, 175 (67.31%) had a low level of sport, 62 (23.85%) had a medium level, and 23 (8.84%) had a high level. Among the 184 senior grade 1 high school students, 107 (58.15%) had a low level of sport, 53 (24.81%) had a medium level, and 24 (13.04%) had a high level. Among the 192 senior grade two students, 115 (59.90%) had a low level of sport, 46 (23.96%) had a medium level, and 31 (16.14%) had a high level. Among the 184 senior grade 3 students, 110 (59.78%) had a low level of sport, 45 (24.46%) had a medium level, and 29 (15.76%) had a high level.

Specific analysis of different levels of sports in senior high school sports

As shown in Tables 3-5, there was no significant difference in gender and grade among high school students of low, medium and high sports levels ($P > 0.05$), indicating that there was no gender and grade difference between high school students at the same sports level. Therefore, the following analysis was performed in three groups of high school students at low, medium and high sports levels to analyze resilience, school adaptability and cell phone addiction tendency.

Effect of level of sport on school adaptability of high school students

There were significant differences in the scores for academic adjustment, peer relationship, school attitude, class activity adjustment, emotional adjustment, conflict in teacher-student relationship, intimacy of teacher-student relationship when comparing low, medium and high levels of sport ($P < 0.05$) (Figure 2A). There were significant differences in the seven dimensions of school adaptability between students with low and medium levels of sport, low and high levels of sport, and medium and high levels of sport ($P < 0.05$).

Effect of level of sport on resilience of high school students

The total scores for goal focus, positive cognition, emotional control, family support, and interpersonal assistance were significantly different between students with low, medium and high levels of sport ($P < 0.05$) (Figure 2B). There were significant differences between these five dimensions when comparing students with low and medium levels of sport, low and high levels of sport, and medium and high levels of sport ($P < 0.05$).

Effect of level of sport on cell phone addiction tendency of high school students

There were significant differences in loss of control, withdrawal, escape, and inefficiency among students with low, medium and high levels of sport ($P < 0.05$) (Figure 2C). There were significant differences in these four dimensions of cell phone addiction tendency between students with low and medium levels of sport, low and high levels of sport, and medium and high levels of sport ($P < 0.05$).

Table 1 Analysis of characteristics of different levels of sport

	Low level (≤ 19 points)	Medium level (20-42 points)	High level (≥ 43 points)	Total
Score (point)				
Intensity	3 (2, 3)	3 (3, 4)	4 (3, 5)	3 (2, 4)
Time	2 (1, 3)	4.0 (3.0, 4.5)	5 (4, 5)	3 (2, 4)
Frequency	3 (2, 4)	3 (3, 4)	4 (4, 5)	3 (2, 4)
Total score	6.0 (0, 13.5)	27 (24, 34)	49 (48, 62)	16 (6, 30)
Gender, *n* (%)				
Male	157 (52.33)	82 (27.33)	61 (20.34)	300 (100.00)
Female	175 (67.31)	62 (23.85)	23 (8.84)	260 (100.00)
Total	332 (59.29)	144 (25.71)	84 (15.00)	560 (100.00)
Grade, *n* (%)				
Senior 1	107 (58.15)	53 (24.81)	24 (13.04)	184 (100.00)
Senior 2	115 (59.90)	46 (23.96)	31 (16.14)	192 (100.00)
Senior 3	110 (59.78)	45 (24.46)	29 (15.76)	184 (100.00)
Total	332 (56.29)	144 (25.71)	84 (15.00)	560 (100.00)

Table 2 Gender differences in sports of high school students

	Male (*n* = 300)	Female (*n* = 260)	*Z*	*P*
Intensity	3 (2, 4)	3 (2, 4)	3.522	< 0.001
Time	3 (2, 4)	3 (2, 4)	3.002	0.003
Frequency	3 (2, 4)	3 (2, 4)	2.438	0.015
Total score	18 (6, 36)	12 (4, 24)	3.520	< 0.001

Table 3 Effect of gender and grade in high school students with low level of sport

	Intensity	Time	Frequency	Total score
Male	3 (2, 4)	2 (1, 3)	3 (2, 4)	6 (0, 12)
Female	2 (2, 3)	2 (2, 3)	3 (2, 3)	6.0 (2.0, 13.5)
Z	1.709	0.656	1.107	0.323
P	0.087	0.512	0.268	0.747
Senior 1	3.0 (2.0, 3.5)	3 (2, 3)	2 (1, 3)	8 (2.5, 15.0)
Senior 2	2 (2, 4)	2 (1, 3)	3 (2, 4)	6 (0, 12)
Senior 3	3 (2, 3)	2 (1, 3)	3 (2, 4)	6 (0, 12)
H	0039	3.391	4.462	1.434
P	0.981	0.183	0.107	0.488

Correlation analysis of level of sport with school adaptability, resilience and cell phone addiction tendency among high school students

Level of sport was positively correlated with school adaptability and resilience ($P < 0.01$); school adaptability was positively correlated with resilience ($P < 0.01$); and cell phone addiction was negatively correlated with sports, school adaptability and resilience ($P < 0.01$) (Table 6).

Table 4 Effect of gender and grade among high school students with medium level of sport

	Intensity	Time	Frequency	Total score
Male	3 (3, 5)	4 (3, 5)	3 (3, 4)	30 (24, 32)
Female	3 (2, 4)	3 (3, 4)	3.5 (3, 4)	24 (24, 36)
Z	0.873	1.144	0.917	0.450
P	0.382	0.253	0.359	0.653
Senior 1	3 (3, 4)	4 (3, 4)	4 (3, 4)	30 (24, 36)
Senior 2	3 (2, 5)	4 (3, 5)	3 (3, 4)	24 (24, 32)
Senior 3	3 (3, 4)	4 (3, 5)	3 (3, 4)	27 (24, 32)
H	0.009	0.436	1.904	2.875
P	0.996	0.804	0.386	0.238

Table 5 Effect of gender and grade among high school students with high level of sport

	Intensity	Time	Frequency	Total score
Male	4 (3, 5)	5 (4, 5)	4 (4, 5)	60 (45, 64)
Female	4 (3, 5)	4 (4, 5)	4 (4, 5)	48 (48, 60)
Z	0.155	0.949	0.268	0.862
P	0.877	0.343	0.788	0.389
Senior 1	4.0 (3.0, 4.5)	5 (4, 5)	4 (3, 5)	48 (45, 60)
Senior 2	4 (3, 5)	5 (4, 5)	4 (4, 5)	50 (48, 62)
Senior 3	4 (3, 5)	5 (4, 5)	4 (4, 5)	60 (48, 64)
H	1.202	0.145	0.095	3.084
P	0.548	0.930	0.954	0.214

Table 6 Correlation analysis of high school students' sports with school adaptability, resilience and cell phone addiction tendency

	Sports	School adaptability	Resilience	Cell phone addiction
Sports	1			
School adaptability	0.761[b]	1		
Resilience	0.765[b]	0.743[b]	1	
Cell phone addiction	-0.747[b]	-0.766[b]	-0.786[b]	1

[b]$P < 0.01$ (two-tailed).

Analysis of the mediating effects of sport and school adaptability, resilience and cell phone addiction among senior high school students

The Bootstrap method was used to test for mediation effect, so as to prove the degree of influence among dependent, independent and mediating variables. The direct effect of sport on cell phone addiction was significant ($P < 0.001$), accounting for 20.51% of the total effect (Figure 3; Table 7). The mediating effect of school adaptability on sport and cell phone addiction was significant ($P < 0.001$), accounting for 17.38% and 35.36% of the total effect value, respectively. School adjustment and resilience had a significant chain-mediated effect between sport and cell phone addiction ($P < 0.001$), accounting for 26.75% of the total effect.

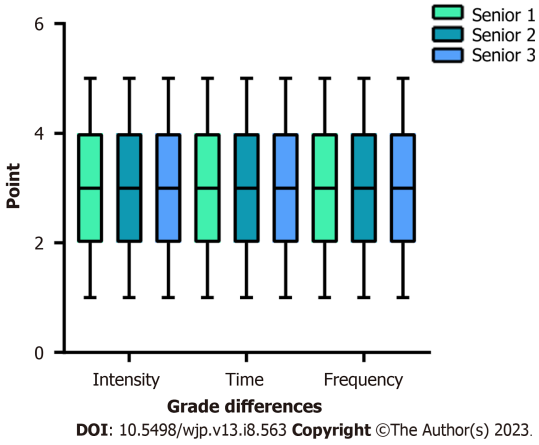
DISCUSSION

We used a field questionnaire survey to collect data on the level of sport, school adaptability, resilience and cell phone

Table 7 Test results of mediating effect

Paths		Coeff	S.E.	LLCI	ULCI
Direct effect	Sports→cell phone addiction	-0.138	0.027	-0.190	-0.085
Indirect effect	(1) Sports→school adaptability→cell phone addiction	-0.117	0.0224	-0.162	-0.0742
	(2) Sports→resilience→cell phone addiction	-0.238	0.025	-0.290	-0.193
	(3) Sports→school adaptability→resilience→cell phone addiction	-0.180	0.017	-0.214	-0.148
	Total indirect effect	-0.536	0.030	-0.598	-0.480
Total effect		-0.673	0.021	-0.714	-0.633

LLCI: Lower limit of 95%CI; ULCI: Upper limit of 95%CI.

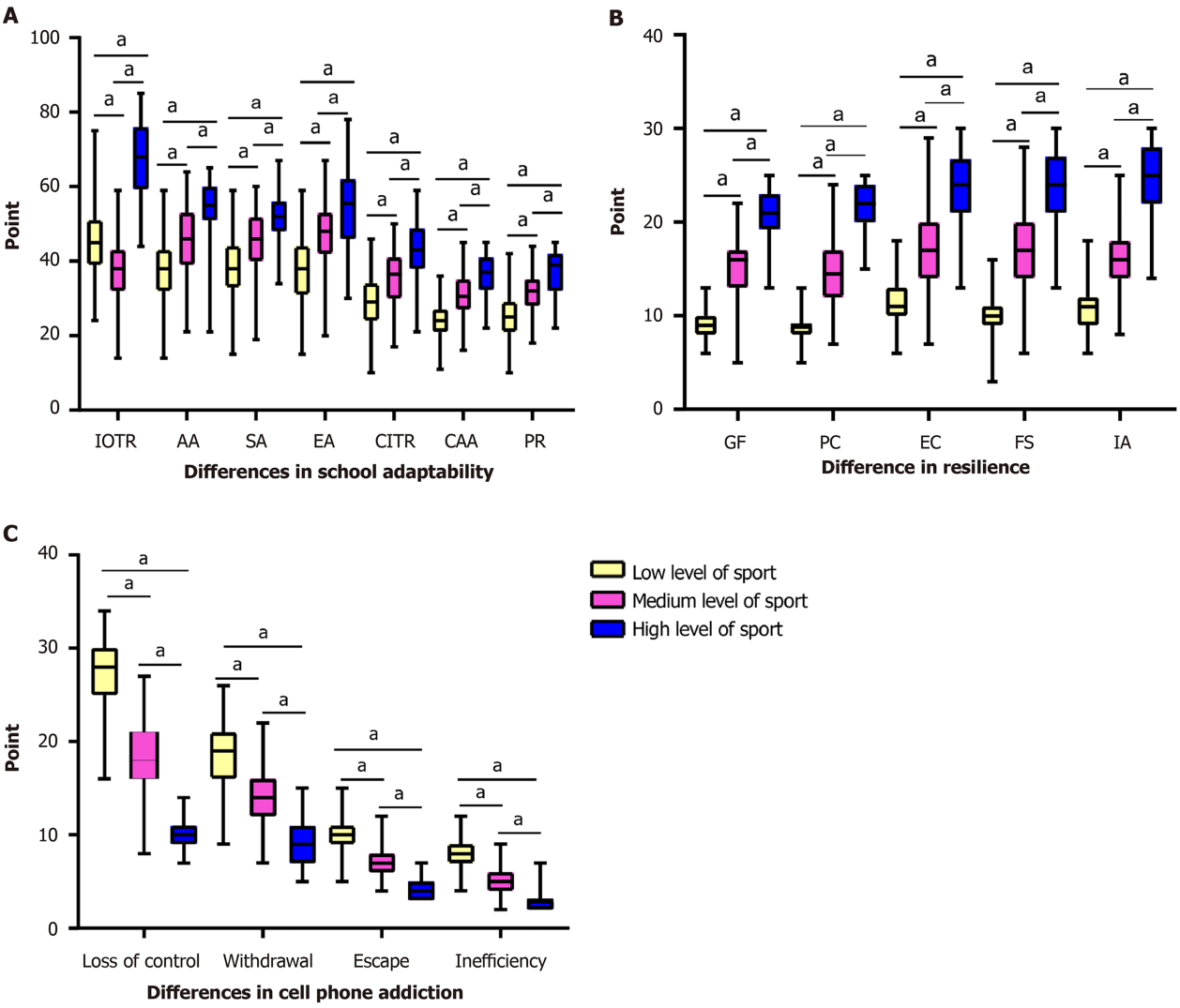


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Figure 1 Differences in level of sport of high school students according to grade.

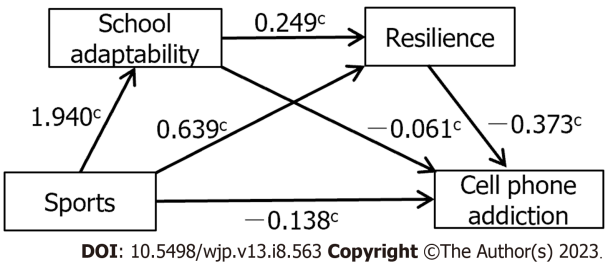
addiction tendency of senior high school students. Through correlation analysis, a chain mediation effect model was constructed to deeply analyze the influence of sports on school adaptability, resilience and cell phone addiction tendency of senior high school students.

The overall level of sport of high school students reached the medium level, and the level of sport differed significantly by gender, but not by grade. In terms of school adaptability, resilience and cell phone addiction tendency, there were significant differences among low, medium and high levels of sport. There was a positive correlation between level of sport, school adaptability and resilience, and a negative correlation between cell phone addiction and level of sport, school adaptability and resilience. Level of sport had a significant direct effect on cell phone addiction, and school adaptability had a significant mediating effect on level of sport and cell phone addiction. There was a significant mediating effect of resilience between level of sport and cell phone addiction. School adjustment and resilience had significant chain-mediated effects between level of sport and cell phone addiction. Previous studies have shown a significant positive correlation between level of sport and school adaptability[16]. This shows that sports can enhance high school students' adaptability to school, help them establish good interpersonal relationships in school, promote their physical and mental health, and better adapt to the school environment. Similarly, other results show that there is a significant positive correlation between sport and resilience[17], indicating that increasing level of sport is the key to improving the resilience of senior high school students[18]. There was also a significant positive correlation between school adaptability and resilience, indicating that high school students with stronger school adaptability had greater resilience. This is conducive for high school students to cope with various difficulties and setbacks encountered in school or life, and to better complete their studies and develop their social ability in the future[19]. A previous study has shown that sports have a significant negative correlation with cell phone addiction tendency of college students[20], and the results of this study show that sports have a significant negative correlation with cell phone addiction tendency of high school students, which is similar to the results of the present study, indicating that sports can indeed improve the extent of cell phone addiction of senior high school students[21]. Sport can enhance the interpersonal interaction between high school students and their peers, teachers and parents, thus enriching their emotional and social needs, so as to reduce the need to use cell phones for social interaction, thereby preventing cell phone addiction[22]. Analysis of the chain mediation effect model of sport, school adaptability, resilience and cell phone addiction showed that the increase in level of sport improved school adaptability of high school students, and their level of resilience, and reduced their cell phone addiction tendency. Increased level of sport also improved high school students' adaptability or resilience, and reduced their cell phone addiction tendency. Improvement of school adaptability is accompanied by improvement of resilience, which can ultimately reduce cell phone addiction tendency of high school students. Therefore, in order to better develop



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Figure 2 Effect of low, medium and high levels of sport. A: On school adaptability of high school students; B: On resilience of high school students; C: On cell phone addiction tendency of high school students. $^{a}P < 0.05$. IOTR: Intimacy of teacher-student relationship; AA: Academic adjustment; SA: School attitude; EA: Emotional adjustment; CITR: Conflict in teacher-student relationship; CAA: Class activity adjustment; PR: Peer relationship; GF: Goal focus; PC: Positive cognition; EC: Emotional control; FS: Family support; IA: Interpersonal assistance.



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Figure 3 Chain mediation effect model. $^{c}P < 0.001$.

the mental and physical health of high school students, schools should raise awareness of the importance of sport. Schools should strengthen sports facilities, provide professional guidance and management of sporting activities, and formulate relevant policies to ensure participation in sport, to help high school students participate in school life in a positive manner, eliminate negative emotions, and enhance ability to withstand pressure. Meanwhile, high school students can reduce their dependence on cell phones and improve their physical and mental development[23].

This study had some limitations. The study sample was not comprehensive enough to represent all high school students, so the results have some limitations. The questionnaire survey was a cross-sectional study, which lacked longit-

udinal data and follow-up survey. The longitudinal data and follow-up survey can be combined to further study the relationship between high school students' level of sport, school adaptability, resilience and cell phone addiction tendency, so as to research on the influence of enriching sports on high school students' school adaptability, resilience and cell phone addiction tendency[24,25].

CONCLUSION

Sport can directly affect school adaptability, resilience and cell phone addiction tendency of senior high school students. Sport can affect cell phone addiction tendency through the mediating effect of school adaptability and resilience, and through the chain mediation effect of both.

ARTICLE HIGHLIGHTS

Research background

High school students are in an important stage of physical development. Sport can promote the healthy physical and mental development of high school students, help them adapt to the school environment, relieve study pressure, reduce the level of stress, and reduce cell phone addiction, which are important for healthy physical and mental development.

Research motivation

This study investigated the influence of sport on school adaptability, resilience and cell phone addiction, to establish whether their relationship had a positive impact on the physical and mental development of high school students.

Research objectives

We investigated the relationship between sport and school adaptability, resilience and cell phone addiction tendency in high school students, and the mediating effect of sport was tested. We hope that this study can strengthen high school students' participation in sport, and indicate new ways for improving school adaptability and resilience and reducing cell phone addiction tendency.

Research methods

We collected data using a field questionnaire survey and SPSS was used to analyze the collected data on the effect of sport, school adaptability, resilience and cell phone addiction tendency in senior high school students. Through correlation analysis, a chain mediation effect model was constructed to analyze the influence of sport on school adaptability, resilience and cell phone addiction tendency of high school students.

Research results

Sport, school adaptability and resilience were positively correlated, while cell phone addiction was negatively correlated with sport, school adaptability and resilience, and sport affected the other three through the chain mediation model. The results provide a theoretical basis for further research combined with longitudinal research.

Research conclusions

We conclude that sport has an impact on school adaptability, cell phone addiction tendency and resilience of high school students.

Research perspectives

We analyzed the effect of sport on school adaptability, resilience and cell phone addiction tendency in high school students. In future research, longitudinal research and follow-up can be combined to analyze the relationship among level of sport, school adaptability, resilience and cell phone addiction tendency.

FOOTNOTES

Author contributions: Zhang LQ and Gao HN designed the research; Zhang LQ performed the research and wrote the paper; both the authors reviewed the paper.

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ORIGINAL ARTICLE

Observational Study

Investigation of contemporary college students' mental health status and construction of a risk prediction model

Xiao-Li Mao, Hong-Mei Chen

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Abstract

BACKGROUND

Due to academic pressure, social relations, and the change of adapting to independent life, college students are under high levels of pressure. Therefore, it is very important to study the mental health problems of college students. Developing a predictive model that can detect early warning signals of college students' mental health risks can help support early intervention and improve overall well-being.

AIM

To investigate college students' present psychological well-being, identify the contributing factors to its decline, and construct a predictive nomogram model.

METHODS

We analyzed the psychological health status of 40874 university students in selected universities in Hubei Province, China from March 1 to 15, 2022, using online questionnaires and random sampling. Factors influencing their mental health were also analyzed using the logistic regression approach, and R4.2.3 software was employed to develop a nomogram model for risk prediction.

RESULTS

We randomly selected 918 valid data and found that 11.3% of college students had psychological problems. The results of the general data survey showed that the mental health problems of doctoral students were more prominent than those of junior college students, and the mental health of students from rural areas was more likely to be abnormal than that of urban students. In addition, students who had experienced significant life events and divorced parents were more likely to have an abnormal status. The abnormal group exhibited significantly higher Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 scores than the healthy group, with these differences being statistically significant ($P < 0.05$). The nomogram prediction model drawn by multivariate analysis includ -ed six predictors: The place of origin, whether they were single children, whether

there were significant life events, parents' marital status, regular exercise, intimate friends, and the PHQ-9 score. The training set demonstrated an area under the receiver operating characteristic (ROC) curve (AUC) of 0.972 [95% confidence interval (CI): 0.947-0.997], a specificity of 0.888 and a sensitivity of 0.972. Similarly, the validation set had a ROC AUC of 0.979 (95%CI: 0.955-1.000), with a specificity of 0.942 and a sensitivity of 0.939. The H-L deviation test result was $\chi^2 = 32.476$, $P = 0.000007$, suggesting that the model calibration was good.

CONCLUSION
In this study, nearly 11.3% of contemporary college students had psychological problems, the risk factors include students from rural areas, divorced parents, non-single children, infrequent exercise, and significant life events.

Key Words: College; Predictive models; Psychological health; Risk factors; Logistic regression analysis; Influencing factors

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Core Tip: Mental health problems in college students have a marked impact on their physical and mental health, and learning capacity, and are also one of the key issues of concern to educators and society. This study analyzed the mental health status of 40874 college students in selected colleges and universities in Hubei Province, China. A logistic regression model was used to explore the factors affecting the mental health of college students. A risk prediction nomogram model was constructed by R software, which improved the visualization and comprehensibility of the research.

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INTRODUCTION

Mental health refers to all aspects and activities of the psyche that are balanced and harmonious, and is manifested in the individual's correct cognition, good mood, and appropriate behavior[1,2]. Research has demonstrated an annual yearly increase in the detection of psychological health issues among college students over the last three years[3], indicating that this problem has attracted more and more attention. In 2017-2018, a white paper study on the mental health of Chinese urban residents showed that 73.6% of the college students surveyed had sub-health status. This problem requires attention in order to be resolved. College students are the backbone of the future of society[4]; with the development of the social economy, competition is becoming increasingly fierce, and the mental health of these students has attracted extensive attention from society and schools[5]. University students are in the transition stage between school and society, and their mental health is highly susceptible to pressure from all sides. Most of the studies on the mental health of college students have mainly focused on the main influencing factors, and there are few studies on risk prediction analysis[6,7]. However, the diversity, complexity, variability, contingency, and uncertainty of college students' mental health problems pose challenges in mental health risk prediction. Therefore, constructing a risk prediction model is conducive to screening mental health problems, preventing and treating risk factors for disease occurrence, and reducing morbidity. This study determined the mental health of current college students using a questionnaire survey. Based on an analysis of influencing factors, a mental health risk prediction model for college students was constructed using logistic regression, which provided a reference for counseling college students' mental health problems in the future, which was conducive for providing better mental health care for college students.

MATERIALS AND METHODS

General information

All college students in some of the universities in Hubei Province were selected as research subjects. An online questionnaire survey was conducted from March 1 to 15, 2022, and the questionnaires were distributed using QQ and WeChat. Based on the principle of voluntariness, the respondents completed the questionnaire after scanning the QR code. Each IP address can only be registered to answer once to ensure the quality of the questionnaire. After the investigation, a total of 41610 survey forms were acquired, of which 40874 data were used, and the effective response rate was 98.2%. In these valid data, girls accounted for 45.4% (18547) and boys accounted for 54.6% (22327). A random sampling method selected 2% of valid questionnaires from 40874 valid data.

Research methods

The general questionnaire included data on age, grade, gender, family situation, academic performance, major life events, and other social demographic data. Using the symptom self-rating scale (SCL-90)[8,9], a total of 90 items were scored at 5 levels (0-4), with scores ranging from 0 (none) to 4 (severe); the scale is divided into physical status, interpersonal sensitivity, obsessive-compulsive symptoms, anxiety, depression, hostility, paranoia, terror, psychosis and another 10 symptoms. This scale is commonly used in mental health screening tools due to its comprehensiveness and ease of understanding. The Patient Health Questionnaire (PHQ-9)[10,11] was used to evaluate depression in college students. There were 9 criteria in total and the scoring ranged from 0 (never) to 3 (almost every day). The total score was the sum of the scores of each item (0-27 points). The score was divided into 5 levels (no depression to severe depression): 0-4, 5-9, 10-14, 15-19, and 20-27. Assessment of generalized anxiety symptoms was carried out using The Generalized Anxiety Disorder score[5], with a total of 7 items (0-3 points: From none to almost always), 4 levels of the total score 0-21 points (no anxiety to severe anxiety: 0-4, 5-9, 10-14, 15-21), and the higher the score, the more pronounced the anxiety state.

Statistical analysis

Statistical analysis was conducted using SPSS23.0 software. The experimental data obeyed normal distribution, expressed as mean ± SD in terms of homogeneity of variance, and were compared by independent samples *t*-test. Count data were expressed as n (%) using the χ^2 test; data with a value of $P < 0.05$ were considered statistically significantly different. Single-factor analysis was performed with SPSS23.0, and logistic regression was used for multivariate analysis of statistically significant variables. The prediction model was then constructed, and a nomogram model was constructed using R4.2.3. This research used the receiver operating characteristic (ROC) curve to predict the model performance and used the H-L to test the goodness of fit of the model.

RESULTS

Sample characteristics

We randomly selected 918 cases consisting of 2% of the valid data, including 814 cases in the mental health group and 104 cases in the abnormal mental health group. The incidence of mental health abnormalities was 11.3%. Educational background, place of origin, parent's marital status, whether they were single children, whether they had significant life events, and whether they had intimate friends showed statistical significance ($P < 0.05$) (Table 1).

Logistic regression analysis

Logistic regression analysis was performed to determine whether mental health was abnormal as the dependent variable (mental health = 0, mental health abnormality = 1) and independent variables comprising factors with a significant statistical correlation or association in single-factor analysis (Table 2). The results showed that parents who were divorced/widowed, non-single children, major life events, infrequent exercise, and no close friends were independent risk factors for mental health abnormalities in college students ($P < 0.05$) (Table 3).

Construction of the nomogram model and validation of its predictive performance

Based on the independent factors in the regression model (education, place of origin, exercise, parents' marital status, close friends, and whether major life events occurred), variables with significant differences ($P < 0.05$) were included and a nomogram model was constructed (Figure 1). The Bootstrap method was used to verify the model. The results of the H-L deviation test were $\chi^2 = 32.476$, $P = 0.000007$, suggesting that the model exhibited favorable calibration. According to the training set, the area under the ROC curve was 0.972 [95% confidence interval (CI): 0.947-0.997], and the specificity and sensitivity were 0.888 and 0.972, respectively. The validation set ROC area under the (AUC) was 0.979 (95%CI: 0.955-1.000), with a specificity of 0.942 and a sensitivity of 0.939. In the training set, the nomogram-based prediction model yielded a mean absolute error (MAE) of 0.01, and the mean square error (MMSE) was 0.00022. The MAE of the validation set was 0.007, and the MMSE was 0.00026. The smaller the statistics, the higher the calibration of the prediction model (Figures 2 and 3).

DISCUSSION

University is an important stage in the life of college students and a crucial period for personality completion and self-improvement[12]. College students are active and accept a wide range of information but do not have complete psychological defense abilities. They are easily disturbed by external factors, causing anxiety, panic, and other negative emotions, resulting in blind conformity and impulsive behavior. For college students, entering university means they are about to enter society. At this crossroad, they face pressure and confusion due to learning, love, employment, and family. These aspects of stress, to a certain extent, affect the psychological health of college students[13]. Due to the increased risk of mental health problems, mental health research has become a priority for many scholars[14]. Studies have found that different nationalities, genders, grades, only children, different subjects, and different school types are all related to the mental health of college students[15]. In addition, some studies have found that only children, parental relationships, and domestic violence directly affect the mental health of college students[16]. These results are not entirely consistent with those of this study. This phenomenon can be explained by the vulnerability of mental health to environmental/social

Table 1 Univariate analysis of the mental health of contemporary college students

Variables	Grouping	Healthy, *n* = 814	Abnormal, *n* = 104	Statistic	*P* value
Age (mean ± SD)		22.98 ± 3.02	23.12 ± 3.16	0.443	0.658
Education, *n* (%)	Specialized	42 (87.50)	6 (12.50)	8.684	0.034
	Undergraduate	629 (92.36)	52 (7.64)		
	Master	116 (76.32)	36 (23.68)		
	Doctor	27 (72.97)	10 (27.03)		
Gender, *n* (%)	Female	317 (90.06)	35 (9.94)	0.952	0.329
	Male	497 (87.81)	69 (12.19)		
Native place, *n* (%)	Countryside	308 (82.35)	66 (17.65)	25.079	< 0.001
	City	506 (93.01)	38 (6.99)		
Nationality, *n* (%)	Han	720 (88.45)	94 (11.55)	0.308	0.579
	Ethnic minority	94 (90.38)	10 (9.62)		
Education level of parents, *n* (%)	Junior high school and below	500 (87.11)	74 (12.89)	5.361	0.069
	Senior high school/technical secondary school	223 (89.92)	25 (10.08)		
	College and above	91 (94.79)	5 (5.21)		
Have major life events occurred, *n* (%)	Yes	36 (36.73)	62 (63.27)	153.396	< 0.001
	No	778 (94.88)	42 (5.12)		
Academic record, *n* (%)	Excellent	38 (86.36)	6 (13.64)	5.378	0.146
	Good	246 (88.81)	31 (11.19)		
	Moderate	493 (89.64)	57 (10.36)		
	Poor	37 (78.72)	10 (21.28)		
Parental marital status, *n* (%)	Normal	622 (93.96)	40 (6.04)	64.313	< 0.001
	Divorced/widowed	192 (75.00)	64 (25.00)		
Only child, *n* (%)	Yes	633 (93.92)	41 (6.08)	69.467	< 0.001
	No	181 (74.18)	63 (25.82)		
Underlying disease, *n* (%)	Yes	698 (87.91)	96 (12.09)	3.306	0.069
	No	116 (93.54)	8 (6.46)		
Take regular exercise, *n* (%)	Yes	371 (93.92)	24 (6.08)	19.054	< 0.001
	No	443 (84.70)	80 (15.30)		
Close friends, *n* (%)	Yes	493 (94.63)	28 (5.37)	42.524	< 0.001
	No	321 (80.86)	76 (19.14)		
PHQ-9 (mean ± SD)		36.29 ± 3.59	42.59 ± 4.35	99.409	< 0.001
GAD-7 (mean ± SD)		32.16 ± 8.13	35.24 ± 6.78	52.650	< 0.001

PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder.

conditions. A survey conducted in the United States found that more than one-third of students suffered from depression, while between 2007 and 2008, approximately 10 percent of college students were found to have considered suicide[17]. According to a study conducted in China in 2010, approximately 10% to 30% of university students were affected by mental health issues, which aligns with the findings of this research. According to the National Mental Health Development Report of China (2019-2020), 18.5% of college students tend towards depression, 4.2% have a high risk of depression, and 8.4% have an anxiety tendency. A sample survey by the former State Education Commission found that 20.3% of college students have psychological problems. The above research results are not entirely different to the results in this study.

Our findings show that parental' divorce/widowhood is a risk factor affecting college students' mental health [odds ratio (OR) = 5.628, (95%CI: 2.450-12.927)]. Family is the crucial environment for personal growth. The family atmosphere

Table 2 Independent variable assignment

Variables	Assignment
Education	Specialized = 0
	Undergraduate = 1
	Master = 2
	Doctor = 3
Only child	No = 1
	Yes = 0
Native place	Countryside = 1
	City = 0
Have major life events occurred	No = 0
	Yes = 1
Take regular exercise	No = 1
	Yes = 0
Parental marital status	Normal = 0
	Divorced/widowed = 1
Close friends	Yes = 0
	No = 1
PHQ-9	Primitive value input
GAD-7	Primitive value input

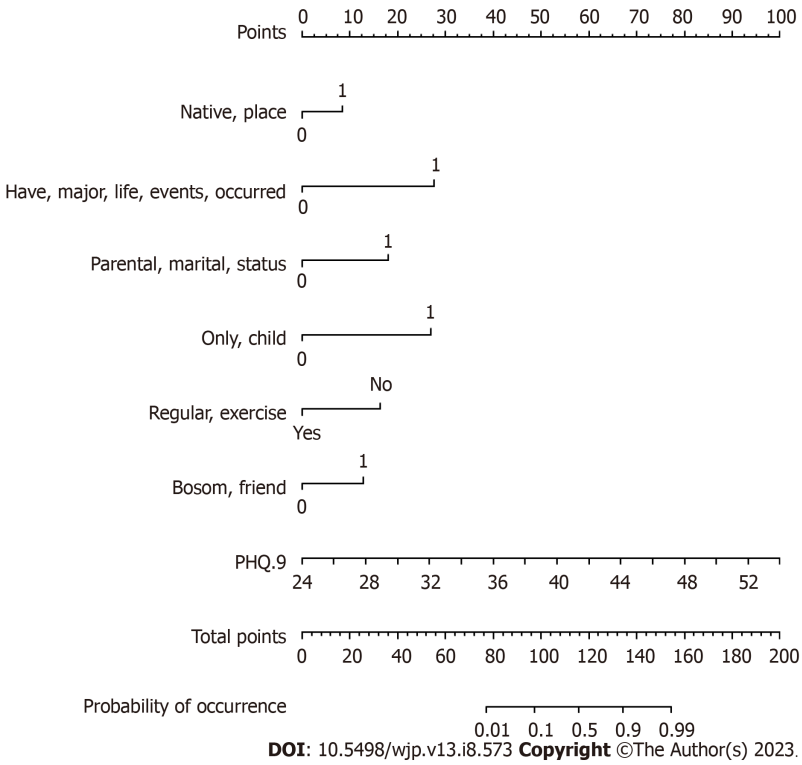
PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder.

Table 3 Logistic regression analysis of the influencing factors on college students' mental health

Variables	β	SE	Wald	*P* value	OR (95%CI)
Education			12.166	0.007	
1	-2.449	1.173	4.357	0.037	0.086 (0.009-0.861)
2	-2.507	0.725	11.957	0.001	0.081 (0.020-0.337)
3	-1.974	0.795	6.168	0.013	0.139 (0.029-0.660)
Native place	1.131	0.419	7.290	0.007	3.099 (1.363-7.043)
Exercise	-2.380	0.554	18.439	0.068	0.093 (0.031-0.274)
Parents' marriage	1.728	0.424	16.597	< 0.001	5.628 (2.450-12.927)
Non-only child	3.616	0.583	38.489	< 0.001	37.175 (11.862-116.500)
Significant events	3.706	0.498	55.318	< 0.001	40.709 (15.329-108.111)
No close friends	1.563	0.443	12.424	< 0.001	4.773 (2.002-11.384)
PHQ-9	0.530	0.061	48.915	< 0.001	1.537 (1.363-1.734)
GAD-7	0.055	0.025	4.014	0.045	1.051 (1.001-1.103)
Constant	-22.220	2.895	58.096	< 0.001	0.000

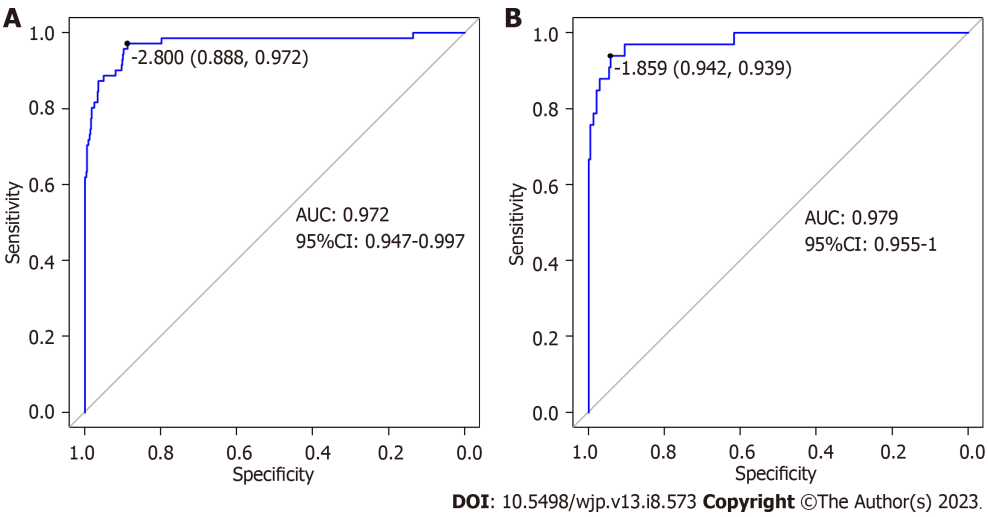
PHQ: Patient Health Questionnaire; GAD: Generalized Anxiety Disorder; OR: Odds ratio; CI: Confidence interval.

significantly relates to the formation of a person's personality[18] and impacts personal psychological development. A large number of research surveys have shown that family has a significant impact on students' mental health[19,20]. A good family environment is conducive to college students' physical and mental health[21], which can reduce the risk of abnormal mental health. An unhealthy family environment (*e.g.*, parental divorce or widowhood, family conflicts) can



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Figure 1 Risk nomogram prediction model of college students' mental health status. PHQ: Patient Health Questionnaire.



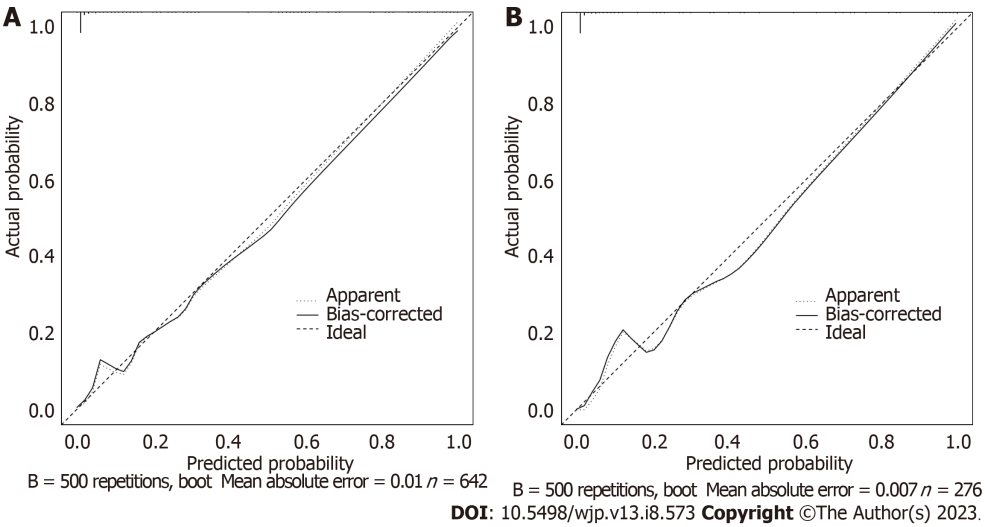
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Figure 2 Column chart prediction model receiver operating characteristic curve. A: Receiver operating characteristic (ROC) curve of the training set; B: ROC curve of the validation set. AUC: Area under the curve; CI: Confidence interval.

easily lead to abnormal mental health in college students and even result in students forming bad personalities[22].

Similarly, studies have shown that parental separation is a risk factor for college students' mental health issues[23]. Domestic and foreign research shows that parental relationships affect children's growth and mental health. Paying attention to the influence of parental relationships on college students' mental health and providing improvement strategies can enable parents to play a role in promoting their mental health.

The present study showed that students from rural areas had an increased risk of mental health issues (OR = 3.099, 95%CI: 1.363-7.043). These results are consistent with those of Zhang and Qi[24]: In terms of psychological stress, college students from rural areas have a significantly higher risk than those from urban areas. These results were related to the rural family's economic environment and cultural atmosphere. Due to differences in resources, the economic conditions of college students from rural areas are worse than those from urban areas. In particular, students from rural areas studying in large cities, have higher living expenses. Some families do not have stable economic sources, and their economic deficiencies and life pressure make them prone to inferiority[25].



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Figure 3 Column chart prediction model calibration curve. A: Calibration curve of the training set; B: Calibration curve of the validation set.

A significant correlation exists between critical life events and the psychological health of university students. In this study, major life events were a risk factor for mental health problems in college students (OR = 40.709, 95%CI: 15.329-108.111). Due to their limited exposure to social and real-life situations, college students are often confined within a sheltered campus environment, lacking sufficient life experience, exhibiting immature cognition, and having insufficient capacity to effectively cope with psychological stressors. When faced with adverse events or unforeseeable circumstances, such as natural disasters or family tragedies, their psychological resilience will be significantly challenged, potentially leading to psychological distress and impediments.

This study showed that regular exercise was a protective factor for mental health (OR = 0.093, 95%CI: 0.031-0.274). Relevant studies have found that moderate physical exercise has a more significant impact on mental health than non-exercise[26]. Fossati *et al*[27] found that participating in sports and exercise benefits an individual's mental state and can improve mood and quality of life. Herbert[28] found that physical activity and exercise help to promote the mental health of emerging adults such as college students. Huang[29] used the intelligent health system to assess the health status of college students before and after dance exercises. The results showed that the mental health of college students participating in dance exercises increased by 7.8%, indicating that sports and dance can promote physical and mental health. Thus, regular exercise can not only promote physical health but also help to improve mental health.

According to the findings of this investigation, a single child has a good mental health status, and being a non-single child is a risk factor for college students' mental health (OR = 37.175, 95%CI: 11.862-116.500). These results are quite different from existing research. Cheng *et al*[30] and others found that the incidence of emotional distress characterized by feelings of unease, apprehension, and low mood in non-single children was higher than that in single children in college and university students from Jinan, Shandong. The reason for this may be that the survey areas were different, and the results do not represent the mental health status of all college students. This may be because most of the single children come from cities, their parents have relatively high educational levels, and their family economic situations are better than those of non-single children. In the one-child family, parents will meet their wishes as much as possible, pay more attention to their education, and get help when they encounter problems. Most of the non-single children were from rural areas, with relatively poor economic conditions and a sense of inferiority[31]; because there are other siblings in the family, parents pay less attention to each child and do not pay attention to communication with their children, resulting in some non-single children encountering problems that cannot be solved and thus affects their mental health.

The findings from this investigation indicated a higher likelihood of psychological problems among college students who lack close friends compared to those who have intimate companions, and was a risk factor for college students' mental health (OR = 4.773, 95%CI: 2.002-11.384). The results by Li *et al*[32] proved this view. Research also shows that good friendships can help people alleviate negative psychology and provide emotional support[33]. The survey by Abraham and Sher[34], it was found that a solid interpersonal relationship was a protective factor against adolescent suicide, which was in line with the findings obtained from the current research: The existence of intimate friends was a protective factor for college students' mental health. In the face of difficulties and pressure, good friends will help and care about each other, which can reduce psychological pressure and is conducive to good mental health. Therefore, getting along with or having close friends is necessary.

The individual is central in resolving their psychological issues. First, they need to develop a scientific understanding of health, proactively foster positive psychological traits, gain accurate comprehension and acceptance of themselves, sustain a favorable emotional outlook, engage with loved ones and acquaintances as support systems when confronting challenges, and cultivate a fully-rounded and harmonious state of health. Secondly, strive to actively acquire and master the techniques for recognizing psychological issues and practicing self-regulation. Individuals should actively exercise, participate in social activities, enrich life experiences, increase social experience, and improve their ability to resist pressure.

Universities and colleges should integrate mental health education into their talent development paradigm by designing courses, organizing psychological quality training sessions, and establishing psychological counseling rooms, among other methods. This would enable college students to acquire knowledge on mental health, enhance their psychological adjustment abilities, and effectively address various psychological issues. In so doing, college students can access timely and effective assistance and guidance during any psychological crises that they may encounter.

Parents ought to lead by example by creating a favorable family environment that fosters effective communication and mutual respect while prioritizing the emotional well-being of their offspring. To achieve this, parents should eagerly listen to their children's emotional needs, encourage them to express themselves fully, and form a close-knit bond with them. They should also aim to foster home-school cooperation towards safeguarding the mental health of college-going students.

CONCLUSION

According to the results of this study, the current college students show a good state in mental health. By using the sample set data of the mental health risk prediction model and modeling and processing it, we provide an important reference for the prevention and intervention of college students' mental health problems. The data obtained from this research is singular, and sourced from a specific region with a limited sample size. As mental health depends on the environment, the representativeness of the sample may have specific limitations. Therefore, it is essential to enhance the model through prospective, multi-center studies with a sufficient sample size.

ARTICLE HIGHLIGHTS

Research background

Mental health problems in college students have become the focus of academic and social attention. The main reason is that college students are facing many pressures and challenges, such as academic pressure, social pressure, career planning pressure, and so on. In addition, the rapid development of modern society and the competitive environment have also brought new challenges and threats to the mental health of college students. Therefore, the study of college students' mental health has profound practical significance and theoretical value.

Research motivation

With the increasing pressure and challenges faced by college students, their mental health problems are becoming more and more serious, and the detection rate is increasing yearly.

Research objectives

Research on the mental health status of current college students and the construction of a risk prediction model can not only help us to understand the mental health problems faced by college students more comprehensively, but also provide a valuable reference for prevention strategies. It can also identify and intervene in mental health problems at an earlier time point to avoid further deterioration of the problem. In addition, future research in this field can also explore the relationship between mental health status and college students' learning, life, and interpersonal communication, and provide useful support for improving the overall quality and development of college students.

Research methods

The objective of the current research was to examine the mental well-being of 40874 undergraduate and graduate students enrolled in various higher education institutions within a particular geographical area. Additionally, using logistic regression analysis, the determinants that exert a substantial influence on the psychological health of university students were investigated. This model has high accuracy and interpretability. This study used R software to construct a risk prediction nomogram model, which enabled researchers to understand the influence and relationship of different variables more intuitively and improved the visualization and comprehensibility of the research. In summary, this study adopted a variety of advanced research methods, which had a wide range of reference values and application prospects.

Research results

The survey found that 11.3% of college students had psychological problems. The risk factors for college students' mental health include being from rural areas, non-single children, major life events, parents' marital divorce, infrequent exercise, and no close friends. The area under the receiver operating characteristic (ROC) curve in the training set was 0.972, the specificity was 0.888, and the sensitivity was 0.972. The area under the ROC curve in the validation set was 0.979, the specificity was 0.942, and the sensitivity was 0.939. These findings reflect the current mental health status of college students and is of great significance for the public to raise attention and awareness of mental health problems. It provides a basis for the government and schools to formulate mental health policies and help to formulate effective mental health management measures. At present, there are still some problems in the design and application of college students' mental health questionnaires, as some students could not understand or answer the questions in the questionnaire. More comprehensive and in-depth analysis and research are still needed to ensure the accuracy and reliability of the analysis

and statistical results.

Research conclusions

From this research, we conclude that the current mental health status of college students is good. New methods used in this study include the use of a logistic regression model and the use of R software to construct a risk prediction nomogram model to explore the related factors affecting the mental health of college students. These methods can predict the risk factors related to college students' mental health more accurately and provide more effective intervention measures and prevention methods.

Research perspectives

Assessing and monitoring the mental health of college students can help schools and other institutions to better understand the needs of college students and take timely measures to prevent the emergence of mental health problems. Future research should focus on developing more effective assessment tools and establishing tracking and monitoring systems.

FOOTNOTES

Author contributions: Mao XL designed and performed the research and wrote the paper; Chen HM designed the research and contributed to the analysis.

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ORIGINAL ARTICLE

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Effect of cognitive behavioral group therapy on rehabilitation of community patients with schizophrenia: A short-term randomized control trial

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Abstract

BACKGROUND

The efficacy of cognitive behavioral group therapy (CBGT) for cognitive dysfunction and negative symptoms of schizophrenia is established, but more evidence is required.

AIM

To assess the effectiveness of CBGT combined with mental health education as a treatment for schizophrenia compared with mental health education alone.

METHODS

In all, 120 schizophrenia out-patients were randomized into CBGT combined with mental health education or single mental health education. The primary outcomes were positive and negative symptoms, cognitive function, excitatory factor, anxiety and depression symptom improvements on the positive and negative syndrome scale score. Secondary outcome measures included social function and drug compliance.

RESULTS

There were significant differences between CBGT combined with mental health education and single mental health education on measures of positive and negative symptoms, cognitive functions, excitatory factor, anxiety and depression symptoms, and social functions. No other significant difference in outcomes was

observed.

CONCLUSION
CBGT combined with mental health education may be relevant beneficial treatment method in reducing symptoms, cognitive and social functions of patients with schizophrenia.

Key Words: Schizophrenia; Cognitive behavioral group therapy; Family members; Social functions; Mental health; Community; Psychological intervention

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Core Tip: Psychological therapies for schizophrenia still deserves to be explored due to its advantages of having comparatively fewer side effects. As one of the different psychological approaches, cognitive behavioral therapy has been proven to be effective in the treatment of schizophrenia with sound evidence. This study provides new insights by adding cognitive behavioral group therapy to the conventional pharmaceutical therapy plus mental health education for the treatment of schizophrenia. It also provides some guidance on developing community rehabilitation models in patients with mental illness.

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INTRODUCTION

Schizophrenia is a serious mental disorder, which can lead to loss of personality, decline in social function and the state of mental disability in various levels. Negative symptoms and cognitive impairment have been found to have a profound impact on long-term outcomes of schizophrenia, but current treatment options are limited. Recent studies have shown that the combination of cognitive behavioral group therapy (CBGT) can improve patient compliance with drug therapy, alleviate psychotic symptoms, reduce recurrence and rehospitalization rates, and improve social function and quality of life in schizophrenia.

This study aims to evaluate the impact of CBGT combined with mental health education on the clinical symptoms, cognitive and social functions and psychological status in patients with schizophrenia on the basis of conventional drug treatment, so as to provide evidence for its application to community rehabilitation for patients with schizophrenia.

MATERIALS AND METHODS

Participants

This was a randomized control trial approved by the Biomedical Ethics Review Committee of Longhua District Chronic Disease Prevention and Treatment Center (Mental Health Center), and obtained the informed consent of family members of the research patients. Participants were recruited from outpatients with schizophrenia. The inclusion criteria included diagnosis of schizophrenia (ICD-10 codes F20.0 to F20.9); 1 to 5 years of disease course with a stable condition; presence of dangerous behavior involving verbal threats; no obvious vandalism; partial recovery of self-knowledge; positive score for positive and negative symptom scale (PANSS) ≤ 49 or negative scale score ≤ 49; social function deficiency screening scale (SDSS) score ≥ 2; aged 19 to 60 years old; higher levels of education than primary school; with at least one guardian; taking second-generation antipsychotics for ≥ 1 year. Inclusion criteria for family members was those who have no mental history. Patients with co-morbidities, other psychiatric disorders (*e.g.*, organic disorders, psychoactive substance-induced psychiatric disorders) or serious physical disorders affecting cognitive functions and family members with speech impairment were excluded from this trial.

Study design

Randomization was conducted using computer-generated random numbers with 120 participants allocated in blocks. These patients were randomly allocated to an intervention group and a control group with 60 patients in each group. The intervention group was subdivided into four groups with 15 patients and their family members in each group receiving CBGT combined with mental health education for 8 wk. The interventions in each group were led by an experienced psychiatrist or psychotherapist trained in CBGT. The control group was only given mental health education courses for 8 wk. The study was reviewed and approved by the Biomedical Ethics Review Committee of the Shenzhen Longhua District Chronic Disease Control Centre (Mental Health Centre) and informed consent was obtained from patients'

families.

Intervention programs

CBGT intervention is divided into four stages: (1) Stage 1 (the first time): The initial stage. The basic task is acceptance and commitment. Members and team leaders get to know each other, understand the troubles in each other's life and communicate with each other, normalize problems, introduce CBGT to group members, set group contracts, set group goals and enhance group cohesiveness; (2) Stage 2 (2nd-3rd): *i.e.*, transition stage. Assist group members to deal with their emotional reactions and conflicts, and promote trust and relationship building. Identify the situations that induce stress and emotional conflicts, and perceive the related assumptions of situations, ideas, emotions and behaviors constructed under the stress situation; Identify and evaluate symptoms and negative cognitions; Examine the evidence to repair negative cognitions, core beliefs and dysfunctional assumptions. In addition, this stage also includes relaxation training, role play, imitation demonstration, resolving emotional conflicts such as anxiety and depression, seeking resource support and increasing self-confidence; (3) Stage 3 (4th-7th): *i.e.*, working stage. Further explore problems and take effective actions to promote the change of members' behaviors. Through psychological education and social skill training, encourage members to observe and imitate, consolidate self-monitoring and self-guidance training during rehabilitation, change distorted thinking patterns and improve self-esteem; and (4) Stage 4 (8th): The end stage. Summarize group experiences, consolidate achievements, encourage team members to use learning experiences in life, solve problems and emotional conflicts, enhance self-confidence, inject hope, and deal with parting emotions.

Outcome measures

The participants were randomly divided into an intervention group (60 cases) and a control group (60 cases). Each patient had his/her one family member to participate in the trial. In addition to antipsychotics and mental health education implemented in the community, patients in the intervention group received CBGT together with their guardians for 8 wk. Patients in the control group only received antipsychotic drugs and mental health. Patient social functions, symptoms of schizophrenia and activities of daily living (ADL) were evaluated by SDSS, PANSS and ADL scale before CBGT treatment, 8 wk and 4 wk after the treatment (*i.e.*, before the intervention, after the intervention and 4 wk after the intervention, respectively). According to the evaluation results of the scale at three time points, the intervention effects of CBGT on patient symptoms and social functions were analyzed.

Primary outcome measures

Primary outcome measures include improvements in symptoms measured by the scale of the PANSS. Using the positive and negative symptom scale, five-factor dimensions of Chinese norm were evaluated: Positive factor, negative factor, cognitive factor, excitatory factor, anxiety and depression factor. Social function is evaluated by SDSS scale.

Two psychiatrists scored 10 patients using PANSS scale, and calculated kappa coefficient = 0.822 through SPSS 22.0. The evaluation of the two doctors is in good agreement and has high consistency.

Secondary outcome measures

The ability to live was assessed by the ability of daily living scale. Medication compliance was evaluated from three types: (1) Complete compliance: Completely follow the doctor's advice for one month; (2) part compliance: Taking medicine for more than 33% course of treatment in a month; and (3) non-compliance: 33% course of treatment in a month with no medication.

Statistical analysis

Statistical analysis was conducted using the SPSS 22.0 software. The rank-sum test and sample independent *t*-test were used for the variable data, and the chi square test was used for the categorical data. Repeated measures ANOVA was used to determine the effects of different intervention modalities on patients' clinical symptoms, social functioning, abilities to perform daily living activities and medication adherence at three different time points: Pre-intervention, post-intervention and 4 wk post-intervention. By analysis of studentized residuals, the data in each group had no outliers (≥ ± 3SD) and followed a normal distribution ($P > 0.05$) according to the Kolmogorov-Smirnov test. The conditions for the sphericity test must be satisfied so that the data could be tested for normality and symmetry with sphericity, and in case the assumption for sphericity was not met, the method of Greenhouse-Geisser (G-G) for correction was used. The test level of $P < 0.05$ was considered statistically significant. It was then determined whether there was an interaction between factors (groups and time points) in the intervention group and the control group. If there was an interaction, *t*-test and one-way ANOVA were required to determine whether there was a separate effect. When a separate effect test was required, test level of $P < 0.05$ was considered statistically significant. If there was no interaction, a main effect test was required to determine whether there was a main effect, with a test level of $P < 0.05$ being statistically significant. A two-by-two comparison was carried out. We used Bonferroni correction for multiple repeated ANOVA testing.

RESULTS

After the treatment and at 4-wk follow-up, none of the 120 patients dropped out.

Participant characteristics

Patients with schizophrenia in both groups had a disease course of 1 to 5 years and were in stable condition. They were treated with second-generation antipsychotics in the community. General data show that the average age of them is 38 years old. There were slightly more women (53.33%) than men (46.67%) in the intervention group, and there were more men (61.67%) than women (38.33%) in the control group. The educational background for the participants is mainly below junior high school. There was no significant difference in age, gender, education level, medical burden and family income between the intervention group and the control group. The baseline characteristics of the participants are presented in Table 1.

The general data (age, gender, education level, medical burden, annual family income) of the family members were analyzed and compared in the two groups. There was no significant difference in general data between the two groups ($P > 0.05$). The baseline characteristics of the sample are presented in Table 2.

Primary outcomes

The overall PANSS score, positive factor score, cognitive factor score, excitatory factor score, anxiety and depression factor score and SDSS score decreased successively in the two groups at three time points. After the intervention and at four weeks after the intervention, the overall PANSS score ($P < 0.05$ and $P < 0.001$, respectively), positive factor score ($P > 0.05$ and $P < 0.001$, respectively), cognitive factor score ($P < 0.05$ and $P < 0.001$, respectively), excitatory factor score ($P > 0.05$ and $P < 0.001$, respectively), the scores of anxiety and depression factors ($P > 0.05$ and $P < 0.001$, respectively) and the overall score of SDSS ($P < 0.01$ and $P < 0.01$, respectively) were significantly different from those before the intervention. After repeated measurement analysis of variance, there was interaction between group and time points in the total overall score of SDSS ($P < 0.05$). After the intervention, there were significant differences between the intervention group and the control group in PANSS total score ($P < 0.05$), positive factor score ($P < 0.05$), cognitive factor score ($P < 0.05$) and SDSS total score ($P < 0.01$). At four weeks after the intervention, there were significant differences between the intervention group and the control group in PANSS total score ($P < 0.01$), excitation factor score ($P < 0.05$), cognitive factor score ($P < 0.01$), anxiety and depression factor score ($P < 0.01$) and SDSS total score ($P < 0.01$). Outcomes are shown in Table 3 and Figure 1.

Secondary outcomes

χ^2-test was performed for medication compliance in the two groups at three time points. The results showed that there was no significant difference between the intervention group and the control group before the intervention ($P > 0.05$). There was no significant difference in medication compliance between the two groups after the intervention and at 4 wk after the intervention ($P > 0.05$). Compared with the control group, the proportion of complete compliance in the intervention group increased slightly (8.34%) after the intervention (83.33%) and at 4 wk after the intervention (91.67%) as presented in Table 4.

DISCUSSION

This is a study to evaluate the effect of CBGT combined with mental health education on community-based rehabilitation of patients with schizophrenia. The main results showed that: (1) Compared with the control group, patients in the intervention group had significantly lower PANSS total scores and five factor scores post-intervention, with negative factor and cognitive factor scores still showing reduction at 4 wk post-intervention; (2) SDSS scores in the intervention group significantly decreased; (3) ADL scores decreased in both groups after the intervention and at 4 wk after the intervention, and the difference was not significant; and (4) there was no significant difference in medication adherence between the intervention group and the control group.

Our findings confirm the ameliorative effect of CBGT on the psychotic symptoms of patients with schizophrenia. Combined with the current situation of community psychiatric rehabilitation management in Shenzhen, the participants of this study are migrant workers in Shenzhen, and as general information shows, this group of population has a low level of education, and nearly half of them do not purse education beyond junior high school with a household income of around 40000 CNY. The migrant workers have medical and social resources availability is restricted and have received relatively little social support. Therefore, the aim of this study is to explore a feasible community-based rehabilitation model for migrant workers. In this study, a comparative analysis of psychiatric symptoms using the five-factor dimension of the PANSS scale Chinese normative model found that 8 wk of CBGT combined with mental health education significantly improved the patients' clinicopathological symptoms and remained effective in improving negative symptoms and cognitive dysfunction after 4 wk of follow-up.

Previous studies have reported inconsistent results on the effectiveness of CBGT in improving positive and negative symptoms of schizophrenia, possibly because different studies have used different evaluation criteria and intervention cycles[1-11]. This study was completed using a modified short-term CBGT format in patients with schizophrenia and their family members, and explored together with patients the reasons for their laziness and reluctance to think and communicate, which were often related to their automatic thoughts such as "I am a useless person", "I will not be welcomed by anyone", "things outside are not interesting", *etc*. Behavioral tests are used, *e.g*. developing a behavioral plan to test the validity of one's beliefs, *e.g*. encouraging one to recall his/her pre-morbid state, self-affirming exceptions and increase self-confidence. When distressing experiences such as hallucinations and delusions of "if I go out, I'll get hurt", coping strategies such as self-symptom monitoring logs and problem solving support are used to alleviate patient feelings of unease and surveillance towards the external environment. Patients are encouraged to think about how they

Table 1 Patient characteristics, *n* (%)

Variables	Control group (*n* = 60)	Intervention group (*n* = 60)	t/χ^2	*P* value
Age (yr)	37.95 ± 10.33	38.47 ± 10.68	0.269	0.788
Gender			2.719	0.099
Male	37 (61.67)	28 (46.67)		
Female	23 (38.33)	32 (53.33)		
Educational level			5.967	0.113
Primary school	10 (16.67)	13 (21.67)		
Junior high school	40 (66.67)	29 (48.33)		
Technical secondary school/high school	8 (13.33)	10 (16.67)		
College/undergraduate	2 (3.33)	8 (13.33)		
Medical burden (CNY)	3300 ± 2700	3000 ± 1600	-0.865	0.389
Annual household income (CNY)	45200 ± 32800	38500 ± 29200	-1.178	0.241

The variable data adopts *t*-test, and the attribute data adopts χ^2 test, n = 60. There was no significant difference between the intervention group and the control group ($P > 0.05$).

Table 2 Family member characteristics, *n* (%)

Variables	Control group (*n* = 60)	Intervention group (*n* = 60)	t/χ^2	*P* value
Age (yr)	43.02 ± 10.44	42.38 ± 9.40	-0.349	0.727
Gender			2.344	0.126
Male	35 (58.33)	43 (71.67)		
Female	25 (41.67)	17 (28.33)		
Educational level			9.226	0.026
Primary school	3 (5.00)	13(21.67)		
Junior high school	40 (66.67)	32 (53.33)		
Technical secondary school/high school	3 (5.00)	6 (10.00)		
College/undergraduate	14 (23.33)	9 (15.00)		
Medical burden (CNY)	3300 ± 2700	3000 ± 1600	-0.865	0.389
Annual household income (CNY)	45200 ± 32800	38500 ± 29200	-1.178	0.241

The variable data adopts *t*-test, and the attribute data adopts χ^2 test, n = 60. There was no significant difference between the intervention group and the control group ($P > 0.05$).

perceive the attitudes and behaviors of others in a situation, and how their performance respond to the patient's behaviors. Patients are encouraged to be friendly to group members (behavioral activation: Greeting, asking for help, *etc*.) and then to observe if the group members are interested in them. Friendly feedback from others encourages patients to be more positive in their interpersonal interactions. When prejudicial attributions and negative self-evaluations such as "I can't do it", "I'm useless", "No one wants to help me", "I'm not the same as others" occur, self-focus is enhanced through family companionship, empathic psychological support, imitative learning among group members, focusing on solving difficult problems, improving self-awareness and insight, and strengthening social skills training. Through positive and effective communication, expressing one's real emotional needs, accessing resource support (family support, peer support and social support), coping with crisis, testing hypotheses in practice and feeling trusted. Recent research has also demonstrated the effectiveness of social skills training in improving negative symptoms[1,12]. Cognitive remediation has a small to moderate beneficial effect on negative symptoms enhancing a positive outcome for cognitive impairment [13,14].

The results showed that combined CBGT and mental health education significantly improved social functioning in patients with schizophrenia, but did not have a significant advantage over single mental health education in improving daily living skills[15]. Related studies found that there were more factors influencing daily living skills, such as executive function (21%), memory and abstract thinking (13.5%), negative symptoms (13%), age of onset and years of education

Table 3 Repeated measures analysis of variance on psychopathology, social function, activities of daily living and psychological condition of family members of patients with schizophrenia

Variables	Control group (n = 60), mean ± SD			Intervention group (n = 60), mean ± SD			Repeated measurement, F-test		
	Before intervention	After intervention	4 wk after intervention	Before intervention	After intervention	4 wk after intervention	Main effect for groups (F, P value, $\eta 2_{partial}$)	Main effect for time points (F, P value, $\eta 2_{partial}$)	Group by time point interaction (F, P value, $\eta 2_{partial}$)
Overall score	101.67 ± 21.48	75.78 ± 19.36	57.90 ± 16.52	97.02 ± 24.40	68.15 ± 18.85	48.72 ± 11.28	F = 5.617, P = 0.019, $\eta 2_{partial}$ = 0.045	F = 344.924, P = 0.000, $\eta 2_{partial}$ = 0.855	F = 0.829, P = 0.439, $\eta 2_{partial}$ = 0.014
Negative factor	35.00 ± 5.42	26.58 ± 5.83	19.77 ± 5.26	32.27 ± 7.48	24.05 ± 6.37	16.45 ± 4.22	F = 9.777, P = 0.002, $\eta 2_{partial}$ = 0.077	F = 452.858, P = 0.000, $\eta 2_{partial}$ = 0.886	F = 0.451, P = 0.638, $\eta 2_{partial}$ = 0.008
Positive factor	14.45 ± 3.50	10.77 ± 3.01	8.07 ± 2.56	13.70 ± 3.53	9.60 ± 2.83	7.40 ± 1.43	F = 3.766, P = 0.055, $\eta 2_{partial}$ = 0.031	F = 243.801, P = 0.000, $\eta 2_{partial}$ = 0.420	F = 0.873, P = 0.420, $\eta 2_{partial}$ = 0.015
Excitatory factor	10.53 ± 3.84	7.45 ± 2.89	5.85 ± 2.28	10.45 ± 3.52	6.85 ± 2.28	5.00 ± 1.29	F = 1.437, P = 0.233, $\eta 2_{partial}$ = 0.012	F = 140.501, P = 0.000, $\eta 2_{partial}$ = 0.451	F = 0.801, P = 0.451, $\eta 2_{partial}$ = 0.014
Cognitive factor	22.75 ± 4.72	17.38 ± 4.35	13.45 ± 3.72	21.37 ± 5.61	15.37 ± 4.25	11.23 ± 2.83	F = 7.751, P = 0.006, $\eta 2_{partial}$ = 0.062	F = 275.171, P = 0.000, $\eta 2_{partial}$ = 0.825	F = 0.505, P = 0.605, $\eta 2_{partial}$ = 0.009
Anxiety and depression factor	18.82 ± 6.04	13.70 ± 5.36	11.15 ± 4.31	18.45 ± 6.61	12.07 ± 4.82	8.77 ± 3.00	F = 3.409, P = 0.067, $\eta 2_{partial}$ = 0.028	F = 153.796, P = 0.000, $\eta 2_{partial}$ = 0.724	F = 2.130, P = 0.123, $\eta 2_{partial}$ = 0.035
SDSS score	12.98 ± 3.55	11.1 ± 3.50	8.72 ± 3.82	12.82 ± 3.03	9.48 ± 3.23	6.18 ± 3.40	F = 5.798, P = 0.018, $\eta 2_{partial}$ = 0.047	F = 593.573, P = 0.000, $\eta 2_{partial}$ = 0.910	F = 30.062, P = 0.000, $\eta 2_{partial}$ = 0.339
ADL score	20.13 ± 8.49	16.78 ± 3.95	16.25 ± 3.23	21.05 ± 8.94	16.90 ± 4.00	16.23 ± 2.99	F = 0.134, P = 0.715, $\eta 2_{partial}$ = 0.001	F = 28.065, P = 0.000, $\eta 2_{partial}$ = 0.324	F = 0.323, P = 0.724, $\eta 2_{partial}$ = 0.005

Repeated measurement ANOVA, n = 60. PANSS: Positive and negative syndrome scale; SDSS: Social function deficiency screening scale; ADL: Activities of daily living.

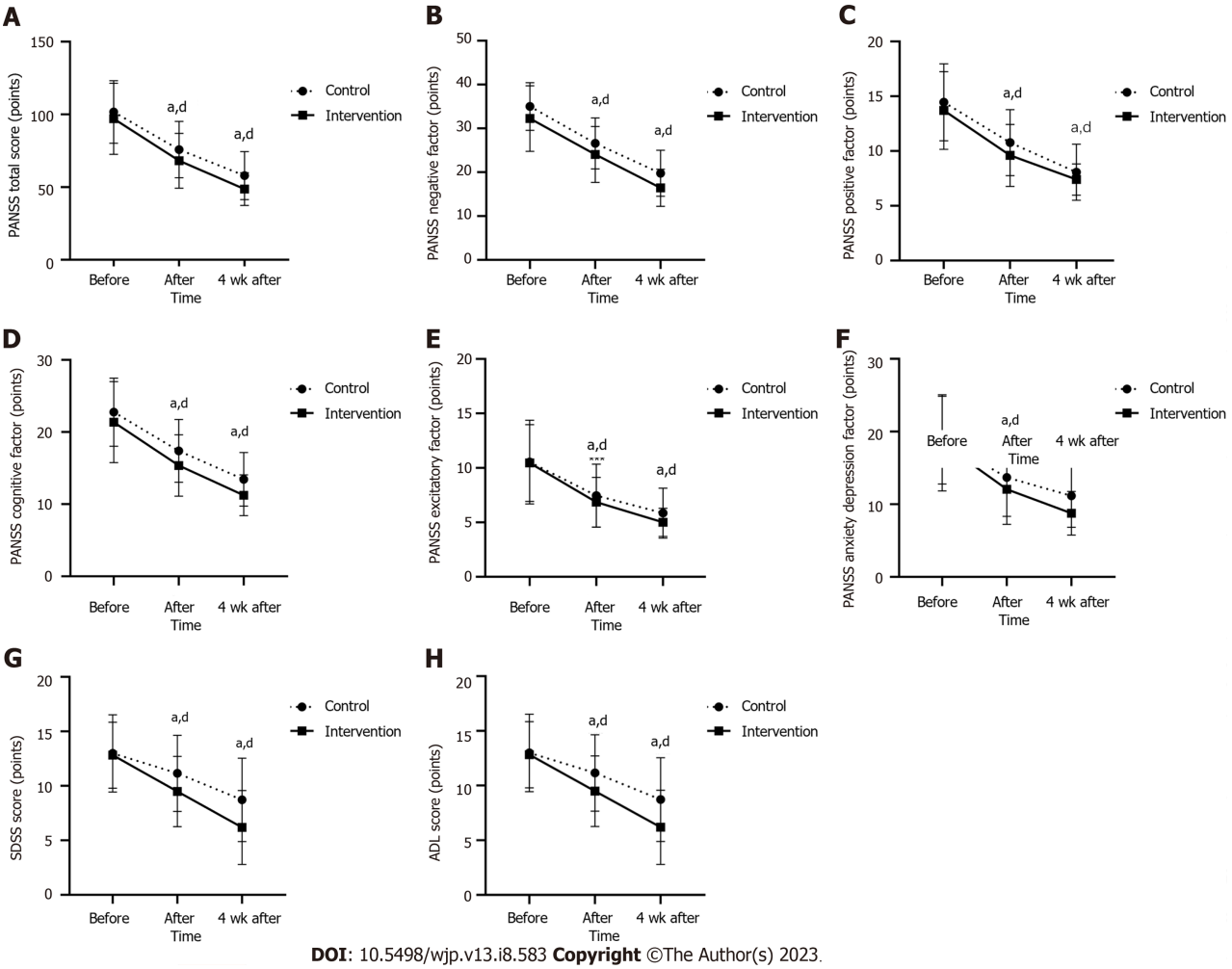
(8%)[16]. This shows that the improvement in cognitive function facilitates the improvement of patient independent living in their communities and issue management in their daily lives. We also saw that the short duration of the intervention and the influence of other related factors, among others, suggest that further research is needed to reveal the effect of CBGT on other factors related to the abilities of schizophrenia patients in their everyday lives.

Furthermore, the results suggest that CBGT combined with mental health education did not have a significant impact on medication adherence in schizophrenia patients, and only slightly increased the proportion of patients who were fully adherent. We can see that outpatients' medication adherence (duration of medication) was more stable under family medication supervision, but we speculate that this may be related to a number of factors influencing adherence, including severity of illness, level of awareness of illness, duration and dosage of medication, family factors, environmental factors, and doctor-patient relationship[17-19]. In future studies, we may need to optimize adherence assessment criteria and will further explore the correlation between adherence and other factors.

We know that treatment with CBGT can have a positive impact on the pathophysiology and cognitive control networks in functional areas of the brain such as the anterior cingulate cortex, dorsolateral striatum, dorsolateral prefrontal cortex, amygdala, basal ganglia, and thalamus, and this evidence provides the basis for a neurobiological brain mechanism for CBGT treatment to relieve negative symptoms and cognitive impairments[20-29]. This study has demonstrated that

Table 4 Medication compliance in the two groups using χ^2 test, *n* (%)

	Pre-intervention compliance		Post-intervention compliance		Compliance at 4 wk after intervention	
	Complete compliance	Partial compliance	Complete compliance	Partial compliance	Complete compliance	Partial compliance
Control group (n = 60)	49 (81.67)	11 (18.33)	48 (80.00)	12 (20.00)	53 (88.33)	7 (11.67)
Intervention group (n = 60)	52 (86.67)	8 (13.33)	50 (83.33)	10 (16.67)	55 (91.67)	5 (8.33)
χ^2	0.563		0.223		0.370	
P value	0.453		0.637		0.543	



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Figure 1 Difference between groups over time using repeated measurement ANOVA. A: Positive and negative symptom scale (PANSS) total score; B: PANSS negative symptom factor score; C: PANSS positive symptom factor score; D: PANSS cognitive factor score; E: PANSS excitatory factor score; F: PANSS anxiety and depression factor score; G: Social function deficiency screening scale score; H: Activity of daily living ADL. [a]P < 0.001 (differences between within-subjects over time using pairwise t test); [d]P < 0.001 (differences between within-subjects over time using pairwise t test). PANSS: Positive and negative syndrome scale; SDSS: Social function deficiency screening scale; ADL: Activity of daily living.

CBGT combined with mental health education intervention improved social functioning, enhanced work drive, interpersonal interactions and cognitive functioning (verbal communication), and reduced positive symptoms, and negative symptoms better than single mental health education in community-rehabilitated schizophrenia patients.

There are some limitations to this study. Firstly, the sample size of this study is relatively small and our findings are preliminary and need to be further validated in an expanded patient sample. Secondly, although the PANSS scale is a screening tool to assess psychopathological symptoms, it cannot further assess quantitative cognitive functions such as executive function, reasoning, attention, verbal-visual learning, and working memory. In future studies, we should select corresponding assessment tools to test the relationship between research CBGT and cognitive impairment. Thirdly, only

the duration of medication was considered when evaluating medication adherence. We need to include other relevant factors (such as disease severity, medication duration and dosing) as measurements to effectively evaluate adherence in patients taking medication regularly in outpatient clinics. Fourthly, this study is a cross-sectional study and suffers from the general limitation of clinician and patient blinding settings that cannot be overcome by CBGT studies, which may lead to a high risk of bias in the assessment results. Further measurements of cognitive function, duration of illness, dosing of medication and other relevant factors are needed in the future to help support the clinical evidence.

CONCLUSION

In conclusion, our data support the view that CBGT combined with mental health education improves clinical symptoms and psychosocial rehabilitation outcomes in people with schizophrenia in the community. Good medication adherence lays the foundation for psychosocial recovery. The degree of family involvement in patient medication supervision has a significant impact on patient psychiatric recovery. Support systems such as family support, peer support and social support are important positive factors for community rehabilitation. Patients can gain social experiences in group-based activity exchanges, gain emotional support and recognition through mutual imitation and learning exchanges, enhance resilience and thus rebuild rational beliefs and strategies, and it also provides some guidance on the development of community rehabilitation models in patients with mental illness.

ARTICLE HIGHLIGHTS

Research background

Cognitive behavioral therapy is an evidence-based adjunctive intervention for schizophrenia and has shown benefits.

Research motivation

Whether the combination therapy of cognitive behavioral group therapy (CBGT) and mental health education shows superior benefits to mental health education alone in the management of schizophrenia?

Research objectives

This study aimed to compare the efficacy of CBGT combined with mental health single mental health education and mental health education alone for schizophrenia.

Research methods

A total of 120 patients with schizophrenia were enrolled and allocated to an intervention group (n = 60) and a control group (n = 60). Patients in the intervention group received CBGT therapy which was added as an adjunctive intervention to antipsychotics and mental health education. Patients in the control group only received antipsychotic drugs and mental health. The cycle of treatment is 8 wk. After a follow-up of four weeks, score for positive and negative symptom scale, social function, activities of daily living and medication compliance were measured.

Research results

It showed that 8 wk of CBGT combined with mental health education significantly alleviated symptoms and cognitive dysfunction and improved social functioning although it did not have a significant impact on medication adherence in patients with schizophrenia after 4 wk of follow-up.

Research conclusions

The results of this study indicate that the combination therapy of CBGT and mental health education is a promising addition to antipsychotics.

Research perspectives

To attain robust results, further large-scale studies should be conducted with the measurements of cognitive function, duration of illness, dosing of medication and other relevant factors are considered to support the clinical evidence.

FOOTNOTES

Author contributions: Chen XL and Deng XT were responsible for study design and data analysis; Sun FG was responsible for data acquirement and mental health education; Chen XL was responsible for cognitive behavioral group therapy; Chen XL and Huang QJ drafted the manuscript and revised it critically; and all the authors critically reviewed the manuscript and gave final approval for its publication.

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SCIENTOMETRICS

Global research trends and mapping knowledge structure of depression in dialysis patients

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Abstract

BACKGROUND

Depression is one of the most common and important psychological issues faced by dialysis patients. It can make it more difficult for them to adhere to their treatment regimen, which, in turn, can worsen their physical symptoms and lead to poorer health outcomes.

AIM

To examine the evolution and growth of publications related to dialysis and depression. The objectives were to identify the number of publications, the top active countries, the contributed institutions, funding agencies and journals, as well as to perform citation and research theme analysis.

METHODS

The search was conducted using the Scopus database for publications related to dialysis and depression between 1970 and 2022. Subsequently, bibliometric analysis was carried out on the data obtained using VOSviewer software, version 1.6.9. This analysis included visualization analysis, co-occurrence analysis and examination of publication trends in dialysis and depression.

RESULTS

We identified 800 publications that met the search criteria. The number of publications related to dialysis and depression has increased significantly in the past two decades. The USA led the way with 144 publications, which is 18% of all publications on this topic. Turkey came second with 88 publications (11%), followed by China with 55 publications (6.88%) and Iran with 52 publications (6.5%). Analysis of the research theme identified three main clusters related to gender differences in prevalence, identification of depression as a risk factor, and effective interventions to relieve depression. Future research direction analysis shows a shift toward effective interventions to relieve depression in dialysis patients.

CONCLUSION
This study provides a comprehensive overview of growth, trends and research themes related to dialysis and depression that could help researchers identify gaps in the literature and develop future research.

Key Words: Dialysis; Depression; Bibliometric; Hot issues; Scopus

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Core tip: Depression is a prevalent psychological problem among dialysis patients, and it can negatively impact their adherence to treatment and health outcomes. A total of 800 publications were identified through a bibliometric analysis of dialysis- and depression-related publications between 1970 and 2022. In the last two decades, there has been a significant increase in the number of publications, and the USA led the way. The identified research themes were gender differences in depression prevalence, the identification of depression as a risk factor, and effective interventions to treat depression. Effective interventions to ameliorate depression in dialysis patients will be the focus of future research endeavors.

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INTRODUCTION

Dialysis is life-sustaining management for patients who have lost renal function due to kidney failure[1,2]. Although it can be an effective treatment for many, it is a complex and demanding procedure that can have significant effects on patients' physical, mental and emotional well-being[3,4]. Depression is a prevalent mental health issue that dialysis users regularly experience[5]. A sensation of despair, hopelessness and helplessness characterizes this syndrome[6]. The stress and ambiguity of treating a chronic illness such as renal failure, as well as the other lifestyle changes that occur alongside dialysis therapy, such as changes to one's diet and daily routine, may all contribute to the onset of depression[7].

According to one study, depression can dramatically affect dialysis patients' quality of life[8]. This can result in psychological and physical symptoms such as weariness, sleeplessness, lack of appetite and loss of interest in previously rewarding activities[9]. Furthermore, depression might make it more difficult for patients to stick to their treatment plan, exacerbating physical symptoms and resulting in poorer health outcomes[10-12]. Several studies have been conducted in recent years to investigate the link between dialysis and depression[13-17]. According to several studies[18-21], depression is more prevalent among dialysis patients than among the general population. Additionally, another study suggests that certain characteristics, such as dialysis duration or changes in dialysis, may increase the incidence of depression[22,23].

A research methodology that studies the organization of academic literature to indicate research trends, patterns and areas of competence is bibliometric and visualization mapping. We may acquire a clearer grasp of the field's structure and geography, identify gaps in knowledge and highlight key contributions by using this methodology to study dialysis and depression[24-27]. This paper reviews the current state of dialysis and depression research, identifies the most influential research publications and institutions and outlines prospective future research directions. It also seeks to provide a complete overview of dialysis and depression research, highlight major research trends and knowledge gaps, and make recommendations for future research. In addition, this study can help researchers to identify voids in the current literature and guide future efforts to advance our understanding of the complex relationship between dialysis and depression.

MATERIALS AND METHODS

Data acquisition

Scopus was chosen to retrieve the publication sources. To avoid potential bias from the daily updates in Scopus, the documents for this study were retrieved and saved on April 12, 2023. The majority of bibliometric studies use Scopus[28-32] and Web of Knowledge[33-35]. Scopus is regarded as the most advantageous database for such analyses due to its numerous benefits[36-40]. Its bibliometric indicators are simple and straightforward. In addition, Scopus includes publications from Medline. Scopus has a number of benefits over Google Scholar and Web of Science. It has a more comprehensive database for bibliometric analysis and covers social sciences and humanities. Its unique characteristics, such as author identification, improve the tracking and evaluation of academics' influence on a particular topic. By offering filtering and sorting options, Scopus facilitates the discovery of relevant research.

Search strategy

A detailed review of the systematic and meta-analysis research on the topic was undertaken to establish the search approach, as referenced in the sources[18-21]. Scopus Engine was used to integrate relevant words connected with dialysis and depression, including Medical Subject Headings from PubMed and prior systematic reviews and meta-analyses. There were four steps in the research strategy. (1) The initial step involved using specific terms and phrases related to dialysis to conduct a title search, which included the following. TITLE ("artificial kidney therapy") OR TITLE (*dialysis*) OR TITLE (extracorporeal therapy) OR TITLE (Hemofiltration) OR TITLE (hemodiafiltration) OR TITLE (hemoperfusion) OR TITLE ("continuous renal replacement therapy"). (2) The second step used specific terms and phrases that are related to depression to conduct a title search that included the following: (TITLE (depress*) OR TITLE (dysthym*) OR TITLE ("seasonal affective") OR TITLE ("bipolar disorder") OR TITLE ("mood disorder*") OR TITLE ("affective disorder")). (3) In the third step, the first two steps were merged and filtered by implementing exclusions and limitations. The search was conducted in Scopus, including articles published up to December 31, 2022, without language restrictions. The research methodology employed the wildcard symbol (*) and quotation marks ("") to refine the search for particular terms or phrases. Errata and retracted documents were excluded from the analysis. (4) The search query resulted was as follows: ((TITLE(depress*) OR TITLE("seasonal affective") OR TITLE(dysthym*) OR TITLE("affective disorder") OR TITLE("mood disorder*") OR TITLE("bipolar disorder")) AND ((TITLE ("Artificial kidney therapy") OR TITLE (*dialysis*) OR TITLE (Extracorporeal therapy) OR TITLE (Hemofiltration) OR TITLE (Hemodiafiltration) OR TITLE (Hemoperfusion) OR TITLE ("Continuous renal replacement therapy")) AND PUBYEAR < 2023)) AND (EXCLUDE (DOCTYPE,"er")).

The search strategy used involved searching for the title using specific keywords rather than searching for both the title and the abstract simultaneously. This approach is considered reliable because it yields minimal false-positive results[41-45]. In contrast, searching for both titles and abstracts may result in a large number of false positives, as the studies' primary focus is on topics other than dialysis and depression.

Validation of the search strategy

The author has taken several steps to ensure the accuracy and reliability of the search query. Firstly, the author improved the query to eliminate false positives. Then, we examined the top 50 most cited papers for relevance to the search subject. Two bibliometric specialists evaluated the title and abstract of these papers and ensured that there were no false positives. The search query was declared complete once it was completed. To confirm that there were no false negatives, the author ran a correlation test between the collected data and the real findings of the field's 20 most active researchers. This test found a strong correlation (r = 0.960) and a significant result (P = 0.001), showing that the search query was precise. This validation method has already been employed in bibliometric studies[46-48]. The rigorous approach and cooperation of two bibliometric specialists enhanced the findings' trustworthiness, and the correlation test gave additional support.

Indices of research productivity

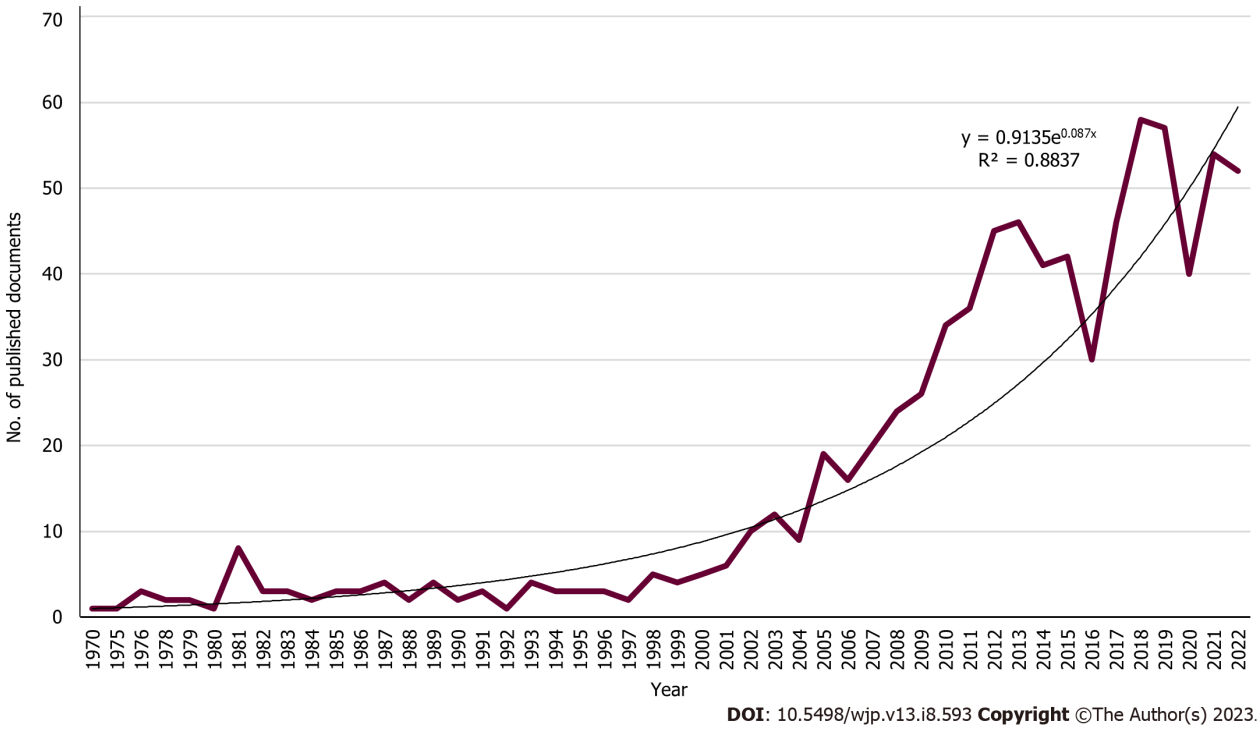
The data collected served as the basis for generating the following information[32,49,50]: (1) Comprehensive analysis and trends of global contributions in publications regarding dialysis and depression from 1970 to 2022; (2) examination of scientific research productivity and collaboration patterns by country; (3) evaluation of research productivity among the most prolific institutions; (4) identification of funding agencies involved; (5) determination of the journals in which international researchers published their work; and (6) assessment of the citations received by these publications.

Bibliometric indicators were utilized to rank the data using the standard competition ranking methodology. Only the top 10 rankings were considered and if two ranking numbers were the same, a gap was left in the subsequent ranking numbers (*e.g.*, 1, 2, 3, 3 and 5)[51]. The quality of research productivity was assessed using the h-index, which represents the number of articles (h) that have received at least h citations[52]. For example, if a researcher has 50 published journal articles, they would have an h-index of 10 if 10 of those papers have received at least 10 citations each and the remaining 40 papers have fewer than 10 citations each. The impact factor was used as an indicator to gauge the importance of the journals, evaluated using the Journal Citation Report (Clarivate Analytics) for the year 2022.

The presented Impact Index per Article refers to the top 10 highly cited papers obtained from the Reference Citation Analysis (RCA) database, which is an open, multidisciplinary citation analysis database owned by Baishideng Publishing Group, located in Pleasanton, CA, USA[53-55].

Visualization analysis

VOSviewer software (version 1.6.9, Leiden University, Leiden, The Netherlands) was used to create network maps depicting the relationships between terms identified in titles or abstracts, as well as cross-national cooperation[56-58]. VOSviewer allows the establishment of knowledge networks by utilizing co-occurrence analysis, which provides a scientific foundation for projecting future research hotspots and following the advancement of various research disciplines[56-58]. By clustering terms based on their co-occurrence, VOSviewer assigns a unique color to each cluster, which can be used to identify and analyze research hotspots more effectively. This approach allows for the visualization and detection of developing trends. Terms are represented as nodes and the associations between them are depicted as lines or links. The thickness of the lines represents the strength of the association between the terms.



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Figure 1 Number of articles analyzed in a bibliometric study on global dialysis and depression-related publications between 1970 and 2022.

RESULTS

Evolution and growth of publications

We identified 800 publications that met the search criteria between 1970 and 2022. Of these, 707 (88.38%) were original research articles, 33 (4.13%) were reviews, 29 (3.63%) were letters to the editor and 31 (3.88%) fell under other categories, such as notes or editorials. The number of publications related to dialysis and depression has increased significantly in the last two decades, with fewer than three articles published annually before 2002. However, since 2013, the number of publications related to dialysis and depression has grown much more rapidly, with more than 46 articles published annually (Figure 1).

Top active countries

In fact, 93 countries have contributed to the literature on dialysis and depression, according to Scopus. The USA led the way with 144 publications, which was 18% of all publications on this topic; Turkey came second with 88 publications (11%), followed by China with 55 publications (6.88%) and Iran with 52 publications (6.5%) (Table 1). Figure 2 depicts the countries with > 10 publications on dialysis and depression, highlighting their collaborative network. The larger the circle, the more publications from that country will be published; and the thicker the line, the stronger the collaboration. The width and number of lines on the map reflect the intensity and degree of interaction between the countries represented. We focused on five VOSviewer clusters to assess their centrality and linkages with other countries. The data are based on a study of 21 countries (as seen in Figure 2), with the USA and Turkey contributing the most publications to the purple cluster.

Contributing institutions

According to Table 2, the top 10 institutions in the study generated a total of 89 publications, representing 11.13% of all the analyzed publications. On examining the papers related to dialysis and depression, the Leids Universitair Medisch Centrum came out on top, producing 18 publications, followed by the Onze Lieve Vrouwe Gasthuis with 14 publications, the VA Medical Center with 13 publications and the University of Hertfordshire with 13 publications.

Contributed funding agencies

Table 3 shows the leading funding agencies according to their production. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institutes of Health (NIH) and the Japan Society for the Promotion of Science (JSPS) emerged as the most productive funding agencies, the NIDDK leading with 26 (3.25%), followed by the NIH with 15 (1.88%) and the JSPS with 11 (1.38%).

Table 1 Top 10 countries ranked by article output on dialysis and depression from 1970 to 2022

Ranking	Country	No. of documents	%
1	USA	144	18.00
2	Turkey	88	11.00
3	China	55	6.88
4	Iran	52	6.50
5	Brazil	42	5.25
5	United Kingdom	42	5.25
7	Japan	38	4.75
8	South Korea	37	4.63
9	Taiwan	35	4.38
10	Canada	25	3.13

Table 2 Top 10 institutions with the highest frequency of article publications on dialysis and depression worldwide, ranked by productivity

Ranking	Institute	Country	No. of documents	%
1	Leids Universitair Medisch Centrum	Netherlands	18	2.25
2	Onze Lieve Vrouwe Gasthuis	Netherlands	14	1.75
3	VA Medical Center	USA	13	1.63
3	University of Hertfordshire	UK	13	1.63
5	Amsterdam UMC	Netherlands	12	1.50
5	The Lister Hospital	UK	12	1.50
5	The University of Jordan	Jordan	12	1.50
8	University of Toronto	Canada	11	1.38
9	The George Washington University	USA	10	1.25
9	King's College London	UK	10	1.25
9	Başkent Üniversitesi	Turkey	10	1.25

Contributing journals

Table 4 lists the top 10 journals ranked by number of publications, which together make up approximately 21.16% of all publications. *International Urology and Nephrology* had the highest number of publications, with 24, followed by *Renal Failure* with 20 publications and *Kidney International* with 16 publications.

Citation analysis

In total, the top 10 articles received 2715 citations, with an average of 271.5 citations per article. The number of citations ranged from 206 to 446[59-68]. Table 5 displays the publications that garnered > 205 citations and were among the top 10. The impact index per article of the 10 most cited articles ranged from 4.9 to 16.6 (Table 5).

Research themes in the literature on dialysis and depression

Figure 3 presents the most commonly used terms in the titles and abstracts of the articles related to dialysis and depression. The size of the circle indicates the frequency of the term, while the distance between two circles or terms indicates their co-occurrence. The terms are grouped based on their close relationship and are represented by different colors. Cluster analysis identified three main clusters, displayed in green, blue and red. The green cluster relates to "gender differences in the prevalence of depression and anxiety among dialysis patients", the red cluster to "identification of depression as a potential risk factor for poor outcomes in dialysis patients", and the blue cluster to "effective interventions to alleviate depression in dialysis patients". The blue cluster was significantly associated with terms from other clusters. Overall, the three clusters are presented in Figure 3.

Table 3 The top ten funding agencies that have the most publications in research related to dialysis and depression from 1970 to 2022

Ranking	Funding agencies	Country	No. of publication	%
1	National Institute of Diabetes and Digestive and Kidney Diseases	USA	26	3.25
2	National Institutes of Health	USA	15	1.88
3	Japan Society for the Promotion of Science	Japan	11	1.38
4	National Center for Advancing Translational Sciences	USA	9	1.13
5	National Heart, Lung, and Blood Institute	USA	8	1.00
5	National Natural Science Foundation of China	China	8	1.00
5	Nierstichting	Netherlands	8	1.00
8	National Institute for Health Research	UK	7	0.88
9	Conselho Nacional de Desenvolvimento Científico e Tecnológico	Brazil	5	0.63
9	National Institute of Mental Health	USA	5	0.63
9	US Department of Veterans Affairs	USA	5	0.63

Table 4 The top 10 journals in research related to dialysis and depression

Ranking	Journal/source title	No. of documents	%	IF[1]
1	*International Urology and Nephrology*	24	3.0	2.266
2	*Renal Failure*	20	2.50	3.222
3	*Kidney International*	16	2.0	18.988
4	*Clinical Journal of the American Society of Nephrology*	15	1.88	10.614
4	*General Hospital Psychiatry*	15	1.88	7.587
4	*Journal of Psychosomatic Research*	15	1.88	4.62
4	*Nephrology Dialysis Transplantation*	15	1.88	7.186
8	*American Journal of Kidney Diseases*	14	1.75	11.072
9	*Hemodialysis International*	13	1.63	1.543
10	*BMC Nephrology*	11	1.38	2.585
10	*Clinical Nephrology*	11	1.38	1.243

[1]Journal Citation Reports (Clarivate, 2022).
IF: Impact factor.

Future research direction analysis

In Figure 4, VOSviewer assigned distinct colors to each term based on the frequency of its appearance in all retrieved publications. Blue was assigned to the terms that first emerged in the literature, whereas yellow was assigned to those that were recently discovered. Before 2014, research in this field focused on the connection between "gender differences in the prevalence of depression and anxiety among dialysis patients" and "identification of depression as a possible risk factor for poor outcomes in dialysis patients". However, the latest research trends, discovered after 2014, revolved around "effective interventions to alleviate depression in dialysis patients".

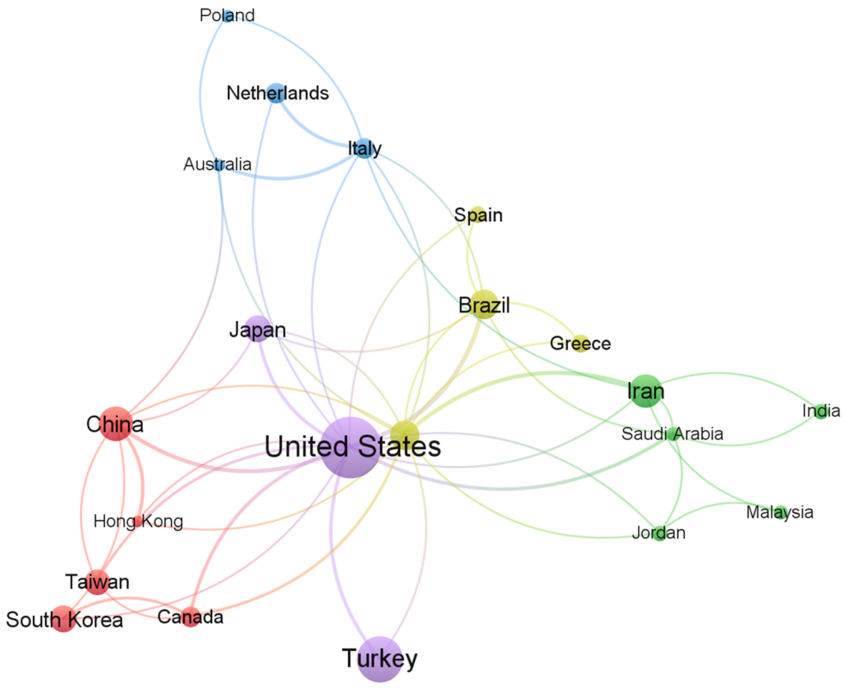
DISCUSSION

Bibliometric analysis is a useful method for evaluating the global research landscape of a specific field. This work's analysis provides insights into the research on depression and dialysis, demonstrating that it has been a topic of interest to scientists worldwide. The prominence of the USA, Turkey and China suggests that these nations may have made distinctive contributions to the discipline. This analysis also yields the identification of notable contributors, such as institutions, journals and funding agencies. These contributors may serve as valuable resources for future researchers seeking collaboration or funding. Identified trends and concentrations in the field of research can help to guide future investigations and inform policy decisions regarding depression and dialysis. Forecasting future developments is also

Table 5 The ten most cited publications in research related to dialysis and depression from 1970 to 2022

Ranking	Ref.	Title	Source title	Cited by	Impact Index Per Article[1]
1	Kimmel *et al*[63], 2000	Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients	*Kidney International*	446	15.7
2	Lopes *et al*[66], 2002	Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe	*Kidney International*	434	16.6
3	Watnick *et al*[67], 2003	The prevalence and treatment of depression among patients starting dialysis	*American Journal of Kidney Diseases*	258	11.1
4	Hedayati *et al*[61], 2006	The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients	*Kidney International*	243	12.1
5	Kimmel *et al*[64], 1993	Survival in hemodialysis patients: The role of depression	*Journal of the American Society of Nephrology*	235	6.7
5	Lopes *et al*[65], 2004	Screening for depression in hemodialysis patients: associations with diagnosis, treatment, and outcomes in the DOPPS.	*Kidney international*	233	10.3
7	Watnick *et al*[68], 2005	Validation of 2 depression screening tools in dialysis patients	*American Journal of Kidney Diseases*	231	11.3
8	Craven *et al*[59], 1988	The Beck Depression Inventory as a screening device for major depression in renal dialysis patients.	*International journal of psychiatry in medicine*	220	4.9
9	Kimmel and Peterson [62], 2005	Depression in end-stage renal disease patients treated with hemodialysis: Tools, correlates, outcomes, and needs	*Seminars in Dialysis*	209	10.8
10	Finkelstein and Finkelstein[60], 2000	Depression in chronic dialysis patients: Assessment and treatment	*Nephrology Dialysis Transplantation*	206	6.6

[1]The Impact Index Per Article is presented based on *Reference Citation Analysis* [Source: Baishideng Publishing Group Inc (Pleasanton, CA 94566, United States)].

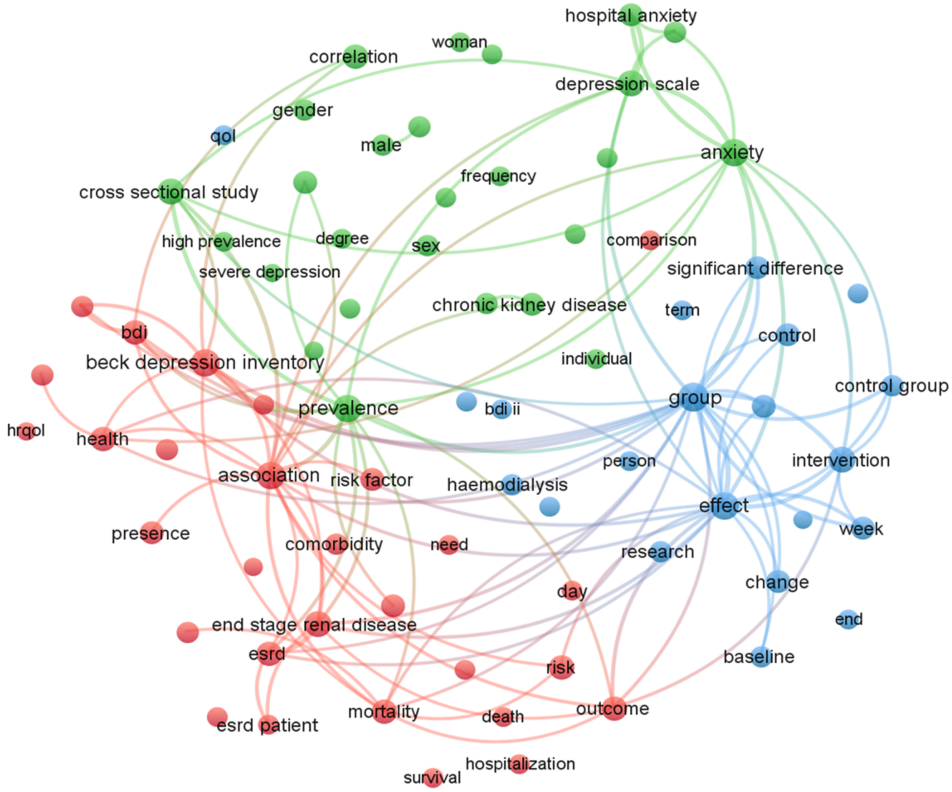


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Figure 2 Visualization of the network of international research collaboration on dialysis and depression among 21 countries with a minimum research output of 10 documents. VOSviewer software version 1.6.19 was used to generate the map.

beneficial for researchers, clinicians and policymakers who wish to anticipate future requirements and plan accordingly.

This study reveals that the amount of research evaluating the literature on dialysis and depression has increased consistently over the past two decades. In the foreseeable future, the amount of research into the connection between



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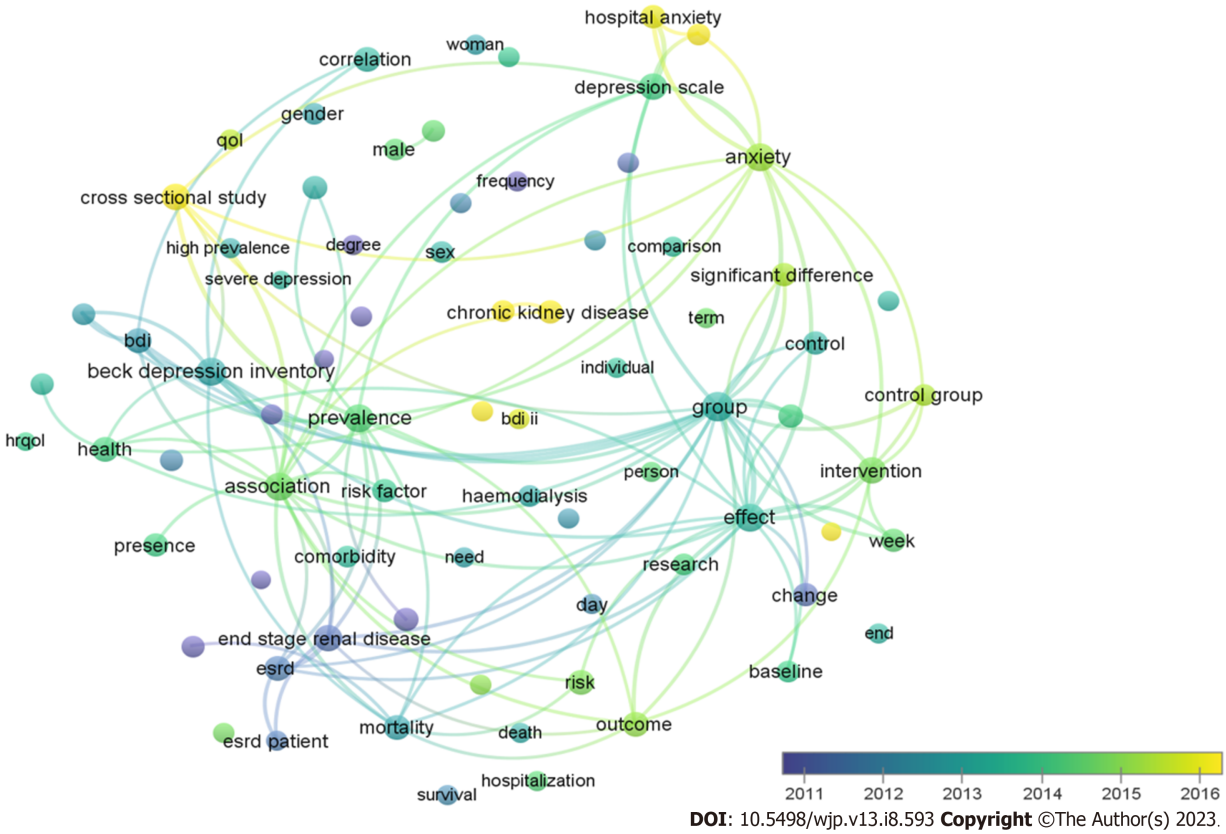
Figure 3 Map visualizing the network analysis of terms found in titles and abstracts, with a minimum frequency of ten or more. Terms are represented as nodes, and the associations between them are depicted as lines or links. The thickness of the lines represents the strength of the association between the terms. VOSviewer software version 1.6.19 was used to generate the map.

dialysis and depression is likely to increase. This is due to the increasing prevalence of chronic kidney disease (CKD) and the fact that depression is a common comorbidity among patients with CKD, especially those who require dialysis[69,70]. Furthermore, there is growing awareness among healthcare professionals of the impact that depression can have on the overall health and well-being of dialysis patients, as well as a greater emphasis on addressing mental health issues as part of comprehensive care[71,72]. As a result, it is reasonable to anticipate that research on this subject will continue to grow in the coming years.

Research studies to identify nations with a significant presence in a specific research discipline. In this case, the USA was determined to have the most influential research on depression and dialysis. This conclusion was likely reached by analyzing the number of publications and citations in these disciplines from various countries. It is not uncommon for countries to excel in particular areas of research while lagging behind in others[73-76]. Variables such as financial resources, government support, academic infrastructure, and cultural attitudes toward research contribute to scientific productivity. Countries such as Turkey, Iran and Brazil may have devoted more resources to depression and dialysis research, resulting in an increase in the number of publications. Additionally, these countries may have research questions or perspectives that have not been investigated as extensively in other regions. Notably, the connection between economic development and scientific productivity is intricate. Although it is true that countries with larger economies typically have more resources for research, there are numerous instances in which smaller or developing countries make significant scientific contributions. However, it is essential to note that research output does not necessarily equate to quality or influence. Other factors, such as funding, collaboration, and the caliber of research institutions, can also affect a country's research influence[77]. It is also possible that other countries conduct high-quality research in these fields but are not recognized due to language barriers or lack of visibility[78].

The main themes of a research paper are usually reflected in the title and abstracts. When the terms depression and dialysis occur together frequently in a research field, it indicates current trends and progress in that area. Based on this cooccurrence, research on depression and dialysis can be categorized into three aspects: (1) "Prevalence of depression and anxiety among dialysis patients and gender differences"; (2) "Identification of depression as a potential risk factor for poor outcomes in dialysis patients"; and (3) "Effective interventions for alleviating depression in dialysis patients".

The prevalence of depression and anxiety among dialysis patients, as well as gender differences, was one of the most important aspects of the study. There are gender differences in the prevalence and presentation of depression and anxiety in this population[79,80]. According to previous studies, women on dialysis are more likely to experience depression and anxiety than men[79-81]. Several factors, including fluctuations in hormones, social roles and cultural norms, might contribute to this[4,82].



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Figure 4 Map of a network visualization analysis of terms in titles and abstracts based on their frequency of appearance. Blue indicates earlier occurrences of the terms, whereas yellow indicates later occurrences. VOSviewer software version 1.6.19 was utilized to create the map.

The second hot topic was the "identification of depression as a potential risk factor for poor outcomes in dialysis patients". According to previous findings, depression in hemodynamic patients is associated with a decline in the quality of life, an increase in mortality and an increase in healthcare costs[11,83-86]. Depression may also be linked to poor adherence to medicine and diet plans, a higher number of hospitalizations and a lack of social support[87]. Healthcare practitioners must be aware of the likelihood of depression in hemodynamic patients and perform routine screenings. Antidepressant drugs, psychotherapy and lifestyle changes can all be used to treat depression in patients[88,89]. Correctly diagnosing and treating depression in these patients can improve both their mental and physical health[88].

The third hot topic was "effective therapies to relieve depression in dialysis patients". Enhancing the quality of life and health outcomes of dialysis patients involves the deployment of depression-fighting therapies[90,91]. Various therapies have been found to be useful for lowering depression in dialysis patients experiencing hemodynamic lysis[19,92,93]. One of the most widely utilized therapies is antidepressant medication. Antidepressant medication has been proven in various studies to be beneficial for reducing depressive symptoms in dialysis patients, as well as for improving other aspects of their health, such as sleep quality and pain management[94,95]. Cognitive behavioral therapy (CBT) is a successful treatment for depression in dialysis patients. CBT is a type of therapy that aims to change negative thought and behavior patterns[96-98]. Several studies have indicated that CBT can considerably reduce depressive symptoms and enhance dialysis patients' quality of life[96,97]. In addition to CBT, exercise, music therapy and mindfulness-based therapies have been demonstrated to be helpful for treating depression in patients[92,99,100]. It has been shown that exercise enhances mood and reduces depressive symptoms in dialysis patients, whereas music therapy and mindfulness-based interventions may be helpful in the management of stress and anxiety.

Most research publications that involved dialysis patients before 2014 focused on the prevalence and gender differences of depression and anxiety and the identification of depression as a risk factor for negative outcomes in those patients. However, a marked change in research trends has been undertaken since 2014. The emphasis has shifted to focus on effective interventions that improve depression in dialysis patients. Thus, the research has acknowledged the value of addressing the practical elements in managing depression and improving the well-being of patients undergoing dialysis. The following future directions in this field are based on these findings. Although this issue to explore gender differences in the prevalence of depression and anxiety among patients undergoing dialysis was prevalent before 2014, further research may be needed for a deeper understanding of the factors that contribute to gender differences and their effects on treatment and outcome. Previous research has focused mainly on studying the correlation between depression and adverse outcomes, but it is necessary to continue to evaluate the relationship and understand the underlying mechanism of depression's impact on the well-being of patients treated with dialysis. Recent articles focus primarily on methods to help people with depression. In the future, researchers should study various treatments such as medication therapies and social support to determine the most effective methods for alleviating depression in these patients.

Research is needed to investigate the psychological and social factors causing depression and anxiety in patients who require dialysis. This involves assessing factors such as economic difficulties, stress management strategies, the presence of strong support systems and other relevant factors that can influence the development and deterioration of depression in this particular patient group. It is essential to acknowledge the lasting effects of therapeutic interventions on the mental and overall health of dialysis patients. By conducting long-term studies and follow-up evaluations, we can gain valuable information regarding the long-term efficacy and sustainability of various treatment approaches.

By utilizing bibliometrics, this study took a novel approach to understanding the academic literature on the relationship between dialysis and depression. Researchers could easily identify study participants, focal areas of interest and emerging patterns within this specific domain by utilizing visual analysis. Although these methods were useful in identifying research trends and knowledge gaps, they did have some limitations. Firstly, there was a potential risk of bias in the selection of publications and the inability to capture the full complexity of research topics. This was mainly due to our search being limited to Scopus, which, although comprehensive and reputable for numerous academic fields, might have omitted papers from alternative sources such as PubMed and Web of Science. Secondly, the list of keywords used in the study was derived from previous literature reviews and it is possible that some keywords were omitted, resulting in false-negative findings. Thirdly, as the citation searches were time dependent, older articles were more likely to be cited, which may have influenced the study findings. Fourthly, the scope of the investigation was limited to the search for the title and specific search phrases related to dialysis and depression, which may have led to the omission of relevant articles that used different terms. Lastly, the limitations of the Scopus database resulted in the dispersion of research output from active institutions with multiple Scopus profiles and the omission of funding agency names due to variations in publication naming conventions. Therefore, it is essential to refrain from manipulating or merging the Scopus output and to restrict data analysis to the specified method.

CONCLUSION

This study investigated the growth, trends and research topics associated with depression in dialysis patients. Analysis of 800 documents published between 1970 and 2022 revealed a significant increase in research activity over the past two decades, emphasizing the significance of addressing this common psychological condition in dialysis patients. In addition to the USA as the main contributor, Turkey, China and Iran have also made substantial contributions to the field. The study identifies key research areas and three major clusters of findings: gender differences in depression distribution; depression as a risk factor; and effective depression treatments. These findings contribute to the knowledge concerning gender-specific depression in dialysis patients and the development of effective strategies to improve their mental health. In addition, this report proposes future research directions, given the increasing emphasis on effective treatments for depression in dialysis patients. The study highlighted the growing awareness of the influence of depression on treatment adherence and health outcomes in this population. This study contributed to the advancement of knowledge in its field by indicating the way forward for future research on depression treatments for dialysis patients.

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ARTICLE HIGHLIGHTS

Research background

Depression is a prevalent psychiatric disorder among patients with end-stage renal disease. Hemodialysis patients have a significantly higher occurrence of depression than the general population. Similar to other chronic illnesses and the overall population, research indicates that depression in hemodialysis patients is linked to a diminished quality of life and heightened mortality.

Research motivation

To identify knowledge gaps and guide future research directions, it is crucial to comprehend the present status of research and areas of focus within the domains of depression and hemodialysis.

Research objectives

The objective of the research was to offer a comprehensive analysis of the existing research in the area of depression and hemodialysis through bibliometric analysis.

Research methods

A search was performed in the Scopus database to find publications on the topic of dialysis and depression from 1970 to

2022. The acquired data underwent bibliometric analysis utilizing VOSviewer software version 1.6.9. This analysis encompassed visualization, co-occurrence, and examination of publication patterns in the field of dialysis and depression.

Research results

The number of publications addressing the correlation between dialysis and depression has increased substantially over the past 20 years. Prior to 2002, the yearly publication count was below three. Nonetheless, starting from 2013, there has been a remarkable acceleration in the publication rate, surpassing 46 articles per year, specifically focusing on dialysis and depression.

Research conclusions

Three significant research topics have emerged, focusing on the varying occurrence of depression and anxiety based on gender, recognizing depression as a contributing factor to negative consequences, and assessing the effectiveness of therapies in reducing depression among individuals undergoing dialysis.

Research perspectives

The objective of this study was to determine present patterns and focal points in the domain of dialysis and depression. This will aid in directing future research and updating clinical practices. Through the utilization of bibliometric analysis, the study offers a thorough summary of the literature concerning this subject matter. Consequently, it facilitates researchers and clinicians in keeping abreast of the most recent advancements in the field.

FOOTNOTES

Author contributions: Al-Jabi SW developed the concept for the manuscript, reviewed the literature, formulated research questions, collected the data, conducted analyses and interpreted the data. The author read and approved the final manuscript.

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Abstract

Deep transcranial magnetic stimulation (DTMS) is a new non-invasive neuromodulation technique based on repetitive transcranial magnetic stimulation technology. The new H-coil has significant advantages in the treatment and mechanism research of psychiatric and neurological disorders. This is due to its deep stimulation site and wide range of action. This paper reviews the clinical progress of DTMS in psychiatric and neurological disorders such as Parkinson's disease, Alzheimer's disease, post-stroke motor dysfunction, aphasia, and other neurological disorders, as well as anxiety, depression, and schizophrenia.

Key Words: Deep transcranial magnetic stimulation; Neurological disorders; Psychiatric disorders; Minireview

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Core Tip: Deep transcranial magnetic stimulation as a novel non-invasive neuromodulation technique has been reported to be applied in clinical psychiatric and neurological disorders. The potential clinical efficacy and safety of this technique in each disorder and the mechanisms behind them need to be further summarized and sorted out, and the direction of future development needs to be more clearly defined.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a magnetic stimulation technique that acts on the cerebral cortex, using electromagnetic principles to deliver an electric field to the cerebral cortex to alter the action potential of cortical nerve cells, thereby regulating metabolism and neural activity in the brain[1]. Repetitive transcranial magnetic stimulation (rTMS) is another form of TMS, which modulates cortical excitability. At high frequencies (> 5 Hz), cortical excitability increases, whereas at low frequencies (1 Hz), a long-term depression effect is produced and cortical excitability decreases [2]. TMS has been widely used to treat several neurological and psychiatric disorders, such as Parkinson's disease (PD), post-stroke limb movement disorders, and depression, with few adverse events. However, conventional TMS has some limitations[3,4], such as limited and imprecise localization of the stimulation site, which has led to the development of deep TMS (DTMS).

DTMS has the advantages of deeper and wider stimulation, more precise localization, and less damage to the superficial cortex than conventional TMS[5,6]. The depth of stimulation can be controlled by adjusting the intensity of the stimulation or the distance between the skull and the coil element. In recent years, this technique has been used to study and treat a variety of neuropsychiatric and psychiatric disorders and has been approved by the Food and Drug Administration (FDA) for the treatment of refractory depression. There has been an increase in national and international research on the use of DTMS in neurological and psychiatric disorders, but there has not been a systematic review of DTMS in the treatment of neurological and psychiatric disorders to evaluate its specific efficacy. This article presents a comprehensive review of the current state of research on DTMS in neurological disorders, such as PD and AD, and psychiatric disorders, such as schizophrenia (SZ) and depression, to provide a reference for future studies.

DTMS IN PSYCHIATRIC DISORDERS

Treatment-resistant depressive

Major depressive disorder (MDD) is one of the most common and disabling psychiatric disorders, with a prevalence of 5%-15% in the general population[7]. Approximately 30% of patients with MDD who do not respond to two or more trials of first-line antidepressants are considered to have treatment-resistant depression (TRD)[8]. TRD is a debilitating chronic mental illness that is associated with increased morbidity and mortality, reduced quality of life, impaired occupational, social, and offspring development, and increased costs on the healthcare system[9]. Currently, depression is mainly treated with medication, but antidepressants tend to be slow-acting and some of the active ingredients in depressants, such as neuropeptides, can be affected by the blood-brain barrier and cause some adverse effects[10].

Studies have shown that an active state of the left dorsolateral prefrontal cortex (PFC) is associated with depressed mood, and improvement of activity levels in the PFC may reduce depressive symptoms. Although TMS is effective in treating depression after stimulation of the dorsolateral PFC[11], there are limitations to this technique, such as the inability to produce some effect in areas such as deeper cortical and limbic areas, where deeper stimulation may be useful. DTMS is an effective new therapy and the FAD has approved the use of DTMS with H1 coils for the treatment of major depression[12]. So far, great results have been achieved with DTMS in the treatment of TRD. The development of DTMS applied to TRD is shown in Table 1.

Levkovitz *et al*[13] conducted a study to examine the impact of high frequency (20 Hz) repeat DTMS on the PFC in 65 patients with non-medicated depression. The researchers discovered that the use of high stimulus intensity resulted in significant improvements in both Hamilton depression rating scale (HDRS) scores and cognitive performance. Notably, no serious adverse events related to the treatment were observed. This study represents a pioneering exploration of the potential of DTMS in addressing psychiatric and neurological disorders[14]. Levkovitz *et al*[15] conducted a pioneering double-blind controlled randomized multicentre study aimed at validating the safety and efficacy of DTMS for the treatment of MDD. The study enrolled a total of 212 outpatients with MDD who had previously experienced treatment failure with antidepressants. The findings revealed a significant improvement in the HDRS-21 score, with a mean increase of 6.39 points in the DTMS group compared to only 3.28 points in the sham control group. Furthermore, the group that underwent DTMS stimulation demonstrated significantly higher rates of response and remission in comparison to the group that received sham stimulation. Moreover, the therapeutic impact of DTMS persisted throughout the 16-wk maintenance phase, proving to be advantageous for patients who had previously shown no response to alternative treatments[15]. The study findings revealed a remission rate of 60% [95% confidence interval (95%CI): 48%-71%] in the DTMS group, whereas the remission rate for rTMS with conventional figure-of-eight coils was 43% (95%CI: 31%-55%) (Table 1)[16-22]. In a meta-analysis conducted in 2019, it was observed that the DTMS group exhibited a response rate of 47.8%, whereas the sham group demonstrated a response rate of 25.6%. Additionally, the remission rate in the DTMS group was found to be 36.6%, while the sham group exhibited a remission rate of 14.8%. The criteria for response were defined as a 50% or greater improvement from baseline, as determined by the primary depression scale used in the study.

Table 1 Development of deep transcranial magnetic stimulation in treatment-resistant depression

Ref.	Method	Result	Adverse events	Significance
Levkovitz *et al*[13], 2009	20 Hz DTMS stimulates FPC	Significant improvement in HDRS scores	Headaches	This is the first time that TRD has been treated with the new H-coil
McGirr *et al* [14], 2014	20 Hz stimulates DLFPC	Reduction in HAMD-21 scores	Unreported	Five-factor personality assessment may have prognostic value in DTMS for resistant MDD
Levkovitz *et al*[15], 2015	20 Hz DTMS stimulates PFC	HDRS-21 score was improved by 6.39 points	Unreported	It is efficacious and safe in patients not responding to antidepressant medications, and the effect remains stable
Feffer *et al* [16], 2017	18 HZ DTMS stimulation; right abductor pollicis brevis muscle	Depressive symptoms (HDRS-21 total score) decreased significantly	Headaches	The severity of the depressive episode is associated with a positive therapeutic effect of dTMS
Kaster *et al* [17], 2018	18 HZ DTMS stimulates DLPFC and VLPFC	Remission rate was significantly higher with active than sham rTMS (40.0% *vs* 14.8%)	Pain and discomfort from stimulus	High-dose DTMS appears to be safe, well tolerated, and efficacious in the treatment of LLD
Tendler *et al* [18], 2018	10 HZ DTMS combined with SSRIs	The remission rate was 35.3%	Headaches	DTMS can augment formerly ineffective SSRI treatment
Filipčić *et al* [19], 2019	18 HZ DTMS stimulates LDLPFC	The response was significantly better in H1-coil than in 8-coil group (OR = 2.33; 95%CI: 1.04-5.21; P = 0.040)	Unreported	DTMS had better response rate than rTMS
Matsuda *et al* [20], 2020	18 Hz DTMS stimulates LDLPFC	HDRS-21 was more significantly improved	Unreported	DTMS might be effective and safe for office workers with treatment-resistant depression
Bahun *et al* [21], 2022	18 Hz stimulates DLFPC	Cognitive function all showed mild to moderate improvement	Unreported	Can improve MDD symptoms

DLFPC: Dorsolateral prefrontal cortex; HDRS-21: Hamilton Depression Rating Scale-21; DTMS: Deep transcranial magnetic stimulation; HAMD-21: 21-item Hamilton Depression Rating Scale; VLPFC: Ventrolateral prefrontal cortex; MDD: Major depressive disorder.

Remission, on the other hand, was defined as a HDRS-17 score of 7 or less, or a HDRS-24 score of 10 or less. Based on these findings, it can be concluded that DTMS is a safe and effective intervention for patients suffering from TRD. Studies combining DTMS and antidepressant medications seemed to show greater therapeutic effects[23].

From the above studies, it is clear that DTMS is an effective treatment for MDD and is well tolerated by patients without major adverse events, and may be a good option for patients who are antidepressant-resistant or ineffective.

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a common and disabling psychiatric disorder characterised by the presence of intrusive thoughts and repetitive behaviors[24], with a lifetime prevalence of 2% to 23%[25]. It is characterised by early onset, which places a heavy burden on patients and their families. Currently, only 40% to 60% of patients can improve certain symptoms with treatment[26]. Studies have shown that the cortico-striatal-thalamic-cortical circuit is dysfunctional in patients with OCD[27], including the orbitofrontal cortex, anterior cingulate cortex (ACC), cingulate cortex, and ventral striatum[28]. A meta-analysis published in 2023 suggested that the average treatment response rate (percentage reduction in total Y-BOCS score) across studies was 39.5% for rTMS and 8.8% for sham conditions. rTMS showed a moderate therapeutic effect (g = 0.65) on OCD symptom severity and a threefold increased likelihood of treatment response (relative risk = 3.15) compared with sham conditions. Greater improvements in comorbid depression severity were associated with greater treatment effects of rTMS on OCD symptom severity. In addition, longer rTMS sessions and fewer total sessions predicted greater clinical improvement[29].

The development of DTMS applied to OCD is shown in Table 2. DTMS was first applied in 2015, when Modirrousta *et al*[30] found that 1-Hz frequency DTMS applied to Brodmann areas 24 and 32 improved OCD symptoms and Yale-Brown-Obsessive-Compulsive Scale (Y-BOCS) scores. In 2018, Carmi *et al*[27] noted a significant increase in Y-BOCS scores with high-frequency (20 Hz) deep magnetic stimulation and the ability to safely and effectively reduce OCD symptoms. They then conducted a prospective multicentre, randomized, double-blind, placebo-controlled trial[31], the results of which showed that patients treated with DTMS had a more significant reduction in OCD symptom scale scores, with an efficacy rate of 38.1%. At the 1-mo follow-up, the efficacy rate increased in both the treatment and sham-stimulation groups, to 45.2% in the treatment group and 17.8% in the sham-stimulation group. In 2018, the United States FDA approved DTMS with the "H7 coil" for the treatment of OCD, potentially for patients for whom medication and psychological interventions have not been effective. Based on previous studies, the response of patients with OCD to DTMS treatment was determined by whether the total score on the Y-BOCS decreased by 30% or more from baseline[32]. We summarised the available studies and found that the remission rate of OCD treated with DTMS was 29.22%-53.90% [31,33,34].

Table 2 Development of deep transcranial magnetic stimulation in obsessive-compulsive disorder

Ref.	Method	Result	Adverse events	Significance
Modirrousta *et al* [30], 2015	1 Hz DTMS stimulates PFC	Improvement in Y-BOCS	Electric shocking sensation	Low frequency deep rTMS was effective in OCD symptom reduction
Carmi *et al*[27], 2018	20 Hz or 1 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	DTMS has the ability to directly modify ACC activity
Carmi *et al*[31], 2019	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	High-frequency DTMS in special region can significantly improve OCD symptoms
Ikawa *et al*[33], 2022	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Slight headache	DTMS treatment of OCD had a favorable therapeutic effect
Ikawa *et al*[33], 2022	20 Hz DTMS stimulates mPFC and ACC	Improvement in Y-BOCS	Electric shocking sensation	DTMS was found to be a safe and effective intervention for OCD symptoms in adolescents

Y-BOCS: Yale-Brown obsessive compulsive scale; mPFC: Medial prefrontal cortex; ACC: Anterior cingulate cortex; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; OCD: Obsessive-compulsive disorder.

Although DTMS is effective in improving OCD symptoms and Y-BOCS scores, the biological basis for the efficacy of DTMS is not yet clear, and more randomised, double-blind, placebo-controlled trials (using dummy coils, at different parameter frequencies) and larger-sample clinical trials are needed to explore this further.

Schizophrenia

SZ, a chronic illness of unknown etiology, is a psychiatric disorder that affects 1% of the world's population[35,36] and may be associated with genetic and environmental risk factors. SZ is often associated with severe impairments in emotions, thinking, and behaviour. A common symptom in people with SZ is hallucinations, which can cause mental debilitation in schizophrenics. Although antipsychotic medications are effective for this symptom, they are still less effective in about 25% of patients. Some studies have shown that hallucinations are associated with increased activity in areas such as the temporal cortex and prefrontal cortex[37], so inhibitory DTMS could be considered to reduce abnormal activity in these areas.

The development of DTMS in SZ is shown in Table 3. DTMS treatment may improve positive symptoms. Rosenberg *et al*[38] conducted an open-label study in which the investigators treated eight patients with SZ diagnosed with persistent hallucinations (hallucinations that had persisted for an average of 11 years) with low-frequency DTMS using an H1 coil, using the Auditory Hallucinations Rating Scale (AHRS) and the Positive Symptom Rating Scale (SAPS) to assess the patients. Five of the patients' AHRS scores decreased by 34.5% and the SAPS score improved by 23.1%. Three patients were subsequently treated with 20 sessions of DTMS, resulting in a 27.8% improvement in AHRS and a 13.75% improvement in SAPS at the end of treatment, and these improvements were maintained over the subsequent 1-mo follow-up period[38]. They then conducted a double-blind study in 2012, in which a total of ten patients completed the treatment and both groups showed an increase in phantom hearing scores, but the difference between the treatment and sham stimulation groups was not statistically significant on either scale[39]. Negative symptoms and cognitive deficits are central to SZ, but current treatments for this condition are underdeveloped. Levkovitz *et al*[40] used DTMS to stimulate the prefrontal cortex of 15 patients with SZ in 2011, and the results obtained 2 wk after treatment showed improvements in both negative symptoms and cognitive function. Some previous studies have suggested that the temporal and parietal cortices are central parts of the language system, that verbal hallucinations may be related to abnormal activity in these regions, and that it may be possible to reduce the hallucination symptoms by suppressing pathological hyperactivity in this region through the use of low-frequency magnetic stimulation[41], but more in-depth studies are needed in the future. In patients with SZ, negative symptoms are often associated with social dysfunction, so it is important to improve negative symptom-based treatment. In 2022, a study of bilateral DTMS of the insula and prefrontal cortex using special H4 coils demonstrated the therapeutic effects of DTMS on psychotic symptoms. In functional magnetic resonance imaging (fMRI) analyses, resting-state connectivity between the insula and the default mode network showed a numerically greater change from baseline in the active DTMS group than in the sham group, consistent with a functional change in insular circuitry[42-44].

Although the current findings on the treatment of negative symptoms with DTMS have shown to be effective, the sample size of the studies is small, and more clinical studies are needed to confirm this in the future. DTMS was also compared to other brain stimulation techniques such as electroconvulsive therapy, transcranial direct current stimulation, vagus nerve stimulation, or standard TMS.

Substance use disorders

Substance use disorders (SUDs) are a group of disorders in which brain damage is caused by chronic use of alcohol and drugs. Substance use disorders are currently difficult to treat, medications are less effective, and the disease has a high relapse rate of 40%-60%[45]. Non-invasive brain stimulation can affect neuroplasticity in the cerebral cortex and throughout the brain, potentially reducing and controlling the compulsive craving for psychoactive substances by rewiring the brain's nerves[46]. Different substance use disorders are affected by similar neural circuits, and because the

Table 3 Development of deep transcranial magnetic stimulation in Schizophrenia

Ref.	Method	Result	Adverse events	Significance
Birdi *et al*[36], 2023	1 Hz DTMS stimulates LTPC	Significant improvement in AHRS score	Transient headache	DTMS treatment was effective for chronic auditory hallucinations in schizophrenic patients
Rosenberg *et al* [38], 2011	20 Hz DTMS stimulates PFC	Cognition and negative symptoms are improved	Transient headache and fatigue	DTMS can improve negative symptoms and cognitive deficits for schizophrenia patients
Rosenberg *et al* [38], 2011	1 Hz DTMS stimulates LTPC	Significant improvement in AHRS score	Mild and self-limiting headaches	DTMS had no significant effect on auditory hallucinations
Rabany *et al*[43], 2014	20 Hz DTMS stimulates PFC	SANS was significantly reduced	Unreported	DTMS was effective for negative symptoms, but the effect was moderate
Linsambarth *et al* [44], 2019	18 Hz DTMS stimulates bilateral PFC	SANS was significantly reduced		DTMS contributed to negative symptoms in schizophrenia
Moeller *et al*[42], 2022	10 HZ DTMS stimulates the insular and prefrontal cortices	The DTMS group had a more pronounced decrease in insula blood flow than the sham operation group	Unreported	DTMS in smoking patients with schizophrenia was effective

AHRS: Auditory Hallucinations Rating Scale; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; SANS: Scale for the Assessment of Negative Symptoms; TPC: Temporoparietal cortex.

use of H-coils can alter the electrical field activity in deep subcortical brain regions, DTMS may be recommended for the treatment of different SUDs.

The evolution of DTMS applied to SUDs is shown in Table 4. Harel *et al*[47] intervened in patients with alcohol use disorders using high-frequency (10 Hz) DTMS and showed that the results were similar to sham. The results showed that the DTMS group had significantly lower levels of alcohol craving and relapse rates of alcohol use disorders compared to the sham-stimulation treatment group. In addition, resting-state network connectivity between the ACC and medial frontal cortex was reduced in the DTMS group during the 3 wk of treatment, and this altered connectivity may be related to substance-induced craving and relapse[47]. Dinur-Klein *et al*[48] evaluated the effects of bilateral prefrontal and insula cortical stimulation using DTMS in patients with nicotine use disorder. The investigators recruited 115 patients with nicotine use disorder (for whom prior treatment had been ineffective), randomizing patients to high-frequency and sham stimulation groups, and showed that high-frequency DTMS treatment significantly reduced patients' nicotine dependence, resulting in a 44% abstinence rate at the end of treatment and a 33% abstinence rate at the 6-mo follow-up, in contrast to the low-frequency DTMS (1 Hz) group, which was less effective[48-50].

In summary, it is clear from the few available studies that high-frequency DTMS may be effective in the acute phase of treatment for some SUD symptoms.

APPLICATION OF DTMS IN NEUROLOGICAL DISEASES

Alzheimer's disease

Alzheimer's disease (AD) is a common and persistent neurological disorder whose prevalence is increasing with the world's aging population. The pathological mechanism of AD may be the structural changes in the brain, abnormal protein deposition, and loss of cholinergic neurotransmission[51]. The functional networks closely related to memory in the brain of AD patients show large-scale disruptions and their plasticity is impaired, as confirmed by neurophysiological and fMRI studies[52]. Currently, there are several disease-modifying therapies such as monoclonal antibodies developed [53]. However, these therapies are specific to early AD stages and amyloid-related imaging abnormalities[54], and there is no effective treatment for AD patients[55]. Gamma oscillations function in information processing by modulating neuronal and glial cell responses to ameliorate AD[56], and pathological increases in gamma band power may be due to the disruption of GABAergic interneuronal networks, resulting in an imbalance between excitation and inhibition in the central nervous system[57]. Brain modulation techniques such as TMS can regulate this unbalanced state of excitation. Recently, brain stimulation to improve cognitive function has received much attention. Chang *et al*[58] first introduced TMS to the motor cortex, and it has now been suggested to be useful in improving cognitive function in AD patients, and the basic principle is that rTMS induces long-term potentiation to enable patients to have enhanced neuronal signaling and increased synaptic plasticity. High-frequency rTMS applied to the dorsolateral prefrontal cortex[59-61] or multiple brain regions[62,63] improves cognition in randomised controlled trials (RCTs) in AD, while functional performance and mood are unaffected[64]. DTMS is still in the early stages of investigation for the treatment of patients with AD.

The evolution of DTMS applied to AD is shown in Table 5. In 2016, Avirame *et al*[65] first applied DTMS to patients with moderate to severe AD, where the researchers used H2 coils to administer 20 DTMS sessions to the PFC of 11 patients with moderate to severe AD, and found that cognitive function improved in 60% to 77% of patients after

Table 4 Development of deep transcranial magnetic stimulation in substance use disorders

Ref.	Method	Result	Adverse events	Significance
Girardi *et al* [49], 2015	20 Hz DTMS stimulates DLFPC	Craving scores dropped significantly	Unreported	DTMS was well tolerated and found to be effective in AUD
Harel *et al* [50], 2022	10 Hz DTMS stimulates mPFC and ACC	A lower percentage of heavy drinking days	Moderate to severe headaches	DTMS was a safe and well-tolerated intervention, with promising initial evidence for efficacy in alcohol addiction

DLFPC: Dorsolateral prefrontal cortex; DTMS: Deep transcranial magnetic stimulation; SUD: Substance use disorders; mPFC: Medial prefrontal; ACC: Anterior cingulate cortices; AUD: Alcohol use disorder.

Table 5 Development of deep transcranial magnetic stimulation in Alzheimer's disease

Ref.	Method	Result	Adverse events	Study design	Significance
Avirame *et al* [65], 2016	10 Hz DTMS for PF stimulation	60%-70% of AD patients' cognitive function was improved	Light headache and occasional tiredness	Case series study	DTMS led to preservation and even improvement of cognitive functions
Leocani *et al* [66], 2020	10 Hz DTMS	ADAS-cog at 4 and 8 wk compared with baseline was improved	Temporary headaches	Double-blind, placebo-controlled pilot study	DTMS was feasible and safe in patients with probable AD

ADAS-cog: Alzheimer's disease assessment scale-cognitive; AD: Alzheimer's disease; DTMS: Deep transcranial magnetic stimulation; PF: Bilateral prefrontal regions.

treatment[65]. A randomized double-blind placebo-controlled trial by Leocani *et al*[66] showed that the DTMS group showed an improvement in AD Assessment Scale-Cognitive (ADAS-cog) scores compared with the sham-stimulation group at weeks 4 and 8 compared with baseline, but this effect diminished after 2 mo of treatment, suggesting that DTMS is effective in AD patients in a short period. However, most of the subjects included in the above two studies were patients with moderate to severe AD for whom DTMS was ineffective in improving cognitive function, and this may be related to the reduced neuroplasticity of the brain in patients with advanced AD. Patients with early AD respond better to DTMS.

Although DTMS is effective in improving cognitive function in AD patients, we need to further validate the efficacy of DTMS combined with cognitive training in early AD patients and conduct more relevant large-scale multicenter RCTs.

Aphasia

Approximately 1/3 of stroke patients are diagnosed with aphasia[67]. Aphasia is an acquired language disorder that has phonological, morphological, semantic, and syntactic deficits that negatively affect patients' functioning, emotions, quality of life, and social participation. Language deficits after stroke aphasia are heterogeneous, and each subtype of aphasia is associated with damage to specific cortical areas, with some extension to subcortical areas[68,69]. Studies have shown that TMS can significantly improve language outcomes in patients with aphasia[70]. H-coil stimulation of a large number of neural networks involved in language function may be more effective than conventional focal coils because of the extensive and non-selective stimulation of language areas in the brain, where aphasia is often due to damage to areas involved in language function[71].

The development of DTMS applied to aphasia is shown in Table 6. First, Spagnolo *et al*[72] utilized repetitive DTMS on a patient diagnosed with progressive supranuclear paralysis accompanied by aphasia. The patient exhibited enhancements across all cognitive domains, particularly in language function. Furthermore, 18-FDG-PET scans revealed notable clinical, neuropsychological, and metabolic improvements when compared to the pre-treatment phase. These findings suggest that DTMS elicits excitation in pertinent functional circuits beyond the intended area of stimulation. Moreover, the observed improvements endured for a minimum of 1 mo post-stimulation, as confirmed through telephone follow-up. In the same year, Trebbastoni *et al*[73] treated a patient with primary progressive aphasia with high-frequency DTMS in the left dorsolateral PFC and showed that the patient also showed transient but significant improvements in verbal fluency and writing ability. Chieffo *et al*[71] suggested that high-frequency DTMS can significantly improve naming ability in patients with chronic post-stroke aphasia.

Although the sample sizes of all the above studies are small and subject to some error, they provide new insights into the use of DTMS in aphasia.

Post-stroke motor dysfunction

Limb motor dysfunction is one of the most common sequelae after stroke. rTMS has been studied to improve motor dysfunction in stroke patients, but the results are somewhat mixed. Some scholars have suggested that an interhemispheric competition model is a basis for rTMS to promote motor recovery after stroke, in which the healthy hemisphere inhibits the diseased hemisphere, resulting in reduced dominance of the hemiplegic limb[74]. In recent years, some of the

Table 6 Development of deep transcranial magnetic stimulation in aphasia

Ref.	Method	Result	Adverse events	Significance
Spagnolo *et al*[72], 2013	10 Hz DTMS stimulates Broca's area and DLPFC	Improvement of language function	Unreported	This observation opens new possibilities for treatment of drug-unresponsive neurodegenerative disorders
Trebbastoni *et al*[73], 2013	hf-rTMS stimulates DLPFC	Improved language in LPPA	Unreported	DTMS improved the linguistic skills
Chieffo *et al*[71], 2014	10 Hz DTMS stimulates Broca's area	Significant improvement in the naming power	Unreported	Deep brain rTMS improved naming in right-handed chronic poststroke aphasic patients

LPPA: Primary progressive aphasia logopenic variant; DLPFC: Dorsolateral prefrontal cortex; DTMS: Deep transcranial magnetic stimulation; hf-rTMS: High frequency-repetitive transcranial magnetic stimulation; rTMS: Repetitive transcranial magnetic stimulation.

above-mentioned scientists have critically proposed a bimodal balance-recovery model, suggesting that the residual structural reserve of the corticospinal tract on the affected side also influences both the hemispheric balance and the degree of functional recovery. Diffusion tensor imaging studies have shown that the integrity of nerve fiber connections between primary and secondary motor areas is positively correlated with recovery of motor function after stroke[75]. DTMS helps to improve motor dysfunction after a stroke.

The development of DTMS applied to post-stroke motor dysfunction is shown in Table 7. Chieffo *et al*[76] applied DTMS to patients with lower limb motor dysfunction after chronic stroke, showing improved lower limb function in patients receiving treatment, and high-frequency DTMS has long-term effects on lower limb motor function in patients with chronic stroke. In 2018, this team again applied DTMS to the rehabilitation of upper limb motor dysfunction after chronic stroke and found that the recovery of upper limb function in patients treated with DTMS combined with exercise training was significantly better than that in patients treated with exercise training combined with sham stimulation, and this effect was more pronounced in patients with severe upper limb motor dysfunction, without serious adverse effects [77].

DTMS is effective in restoring motor function in the limbs after stroke, but the exact mechanism of action remains to be explored. Does DTMS somehow improve the language of patients with aphasia? At this time, we have not found any studies to provide a reference. Existing studies show clinically beneficial effects of TMS with or without combined speech and language therapy on overall language function and expressive language (including naming, repetition, writing, and comprehension) in patients with post-stroke aphasia[70]. In the assessment of aphasia and why not in aphasia therapy, spontaneous and semi-spontaneous speech analysis may be useful[78]. We recommend that future DTMS research on aphasia could be more involved in this gap area.

PD

PD is the second most common neurodegenerative disease in the world, and patients most commonly suffer from abnormal motor symptoms due to the loss of dopaminergic neurons in the substantia nigra[79]. The gold standard treatment for PD is oral levodopa, but the long-term efficacy of levodopa is mostly not maintained[80]. Some reports suggest that the excitability of cortical-mediated pathways may be altered in PD patients, resulting in dyskinesia[81]. Several studies have shown that stimulation of the motor cortex with high-frequency rTMS can improve dyskinesia in PD patients and that the effects can be sustained for a longer period of time[82]. However, some studies suggest that cortical inhibition is impaired in PD patients[83] and perhaps low-frequency stimulation may be more beneficial for PD patients, whereas DTMS is used to act on a wider range of cortical and deeper brain areas.

The development of DTMS applied to PD is shown in Table 8. In 2013, by treating 27 PD patients with movement and high-frequency rDTMS to the prefrontal cortex, Spagnolo *et al*[84] found that the Unified PD Scale (UPDRS) score of PD patients improved significantly after treatment compared to before treatment. Spagnolo *et al*[85] conducted a randomized, sham-controlled trial to evaluate whether high-frequency TMS with an H5 coil is safe and effective for PD patients, and the results showed that patients who received rTMS (M1-PFC and M1 combination) had better results in tremor and hemilateral scores than those in the sham stimulation group. There was no significant difference in safety and efficacy between the two groups, suggesting that gh-frequency rTMS with the H-coil is a safe and effective intervention. It has been suggested that high-frequency rTMS acting on the M1 or PFC may, on the one hand, induce the release of endogenous dopamine in the ipsilateral dorsal striatum[86]. On the other hand, it may promote the production of dopaminergic neurons[87-90].

Studies today have shown that PD patients tolerate DTMS well and no serious adverse effects have been reported in these patients, but there are still some side effects such as transient headache, dizziness, and involuntary movements. However, DTMS can be used to improve the symptoms of dyskinesia in PD patients, and high-frequency stimulation may be more effective than low-frequency stimulation. In the future, RCTs with larger sample sizes and long-term follow-up are needed to determine the optimal treatment parameters and duration of the effect of DTMS.

Table 7 Development of deep transcranial magnetic stimulation in post-stroke motor dysfunction

Ref.	Method	Result	Adverse events	Significance
Chieffo *et al* [76], 2014	20 Hz DTMS	Significant improvement in lower limb motor function	Unreported	DTMS could induce improvements in lower limb functions in the chronic post-stroke period
Chieffo *et al* [77], 2018	20 Hz DTMS	Upper limb motor function improved significantly	Transitory dizziness, toothache, and muscle twitches	DTMS combined with exercise training is more effective (upper limb motor function)

DTMS: Deep transcranial magnetic stimulation.

Table 8 Development of deep transcranial magnetic stimulation in Parkinson's disease

Ref.	Method	Result	Adverse events	Significance
Spagnolo *et al* [84], 2014	10 Hz DTMS for PF stimulation	UPDRS was improved	Slight and transitory hypotension and headache	DTMS might be a safe treatment for PD motor symptoms
Cohen *et al*[87], 2018	M1 + PFC or M1	M1 + PFC OR M1 group was improved in T-UPDRS and M-UPDRS	Mild and transient head discomfort, transient fatigue, and rare mild visual transient hallucinations during stimulation	DTMS improved PD motor symptoms but the effect was moderate
Torres *et al*[80], 2015	M1 + PFC	UPDRS was improved	Sleepiness, headaches, and nausea	DTMS improved motor, postural, and motivational symptoms of PD patients
Cohen *et al*[88], 2016	1 Hz DTMS M1 and 10 Hz DTMS PFC	UPDRS was improved	Headache, dizziness, pain in the head or neck during treatment; nausea, general weakness, and transient aggravation of gait disturbance	DTMS improved motor, but no advantage compared to sham treatment
Spagnolo *et al* [85], 2020	M1 + PFC or M1	UPDRS was improved	Mild, not-distressing, and transient dyskinesias	DTMS was a safe and potentially effective procedure
Cohen *et al*[87], 2018	1 Hz M1 or 10 Hz PFC	UPDRS was improved	Headache, nausea, and discomfort of the eye region or tearing of the eyes during stimulation	DTMS can decrease the subjective motor symptom severity and depression

PF: Bilateral prefrontal regions; M1 + PFC: Sequential stimulation of low frequency over the primary motor cortex and then high frequency over the prefrontal cortex; M1: Low-frequency stimulation over the primary motor cortex alone; UPDRS: Unified Parkinson's Disease Rating Scale; M-UPDRS: Motor UPDRS; T-UPDRS: Total UPDRS; DTMS: Deep transcranial magnetic stimulation; PFC: Prefrontal cortex; PD: Parkinson's disease.

DISCUSSION

The results of our review suggest that the DTMS technique is safe and effective when applied to various neurological and psychiatric disorders, with no serious adverse effects identified other than transient headache and fatigue. However, the biology of the efficacy of DTMS is not yet clear, so its efficacy is mostly assessed by psychometric scales such as the UPDRS and HDRS-24[13], and biological indicators are lacking. A comparison of DTMS with other brain stimulation techniques[90] such as magnetic shock therapy, electroconvulsive therapy[91], transcranial direct current stimulation, vagus nerve stimulation, or deep brain stimulation would provide better clinical evidence for patients.

The advantage of DTMS over conventional TMS is that the H-coil can stimulate deeper areas of the brain without increasing the intensity of the stimulation[92], thus ensuring the continuous stimulating effect of DTMS. There are currently more than 20 H-coils available, of which the H1/H2 coil is FDA cleared for bilateral PFC stimulation. DTMS can stimulate deeper and wider areas of the brain and modulate neurological function through the H-coil, which is effective and safe in the treatment of PD, AD, SZ, and depression. Based on the above tables, it can be seen that DTMS is currently most commonly used in PD, OCD, and depression, with high levels of patient acceptance and efficacy. Some of the other neurological and psychiatric disorders treated with DTMS are still in the early stages of research, and although some have shown significant efficacy, more research is needed to validate them in the future. It is believed that with the continued optimization of the DTMS coil device and further understanding of the etiology of neurological and psychiatric disorders, as well as the resolution of some ethical and legal issues related to these disorders, the use of DTMS with different coils and parameters for different disorders can be explored in the future, thus creating a standardized treatment plan for patients with different disorders, which will facilitate the treatment of patients who have failed or cannot take medication for a long time. This will facilitate the use of DTMS for patients who have been on medication for a long time or are unable to take medication.

CONCLUSION

A large number of studies have shown that DTMS technology is generally safe and tolerable, with mild side effects, and can be used to rehabilitate mental and nervous system disorders. DTMS regulates neural function by directly stimulating deeper and wider brain regions, and currently the evidence for DTMS in the treatment of depression and OCD should be strong. However, for other neurological disorders (particularly neurodegenerative disorders), there are very preliminary results and small sample sizes. RCTs with larger sample sizes should be warranted.

However, DTMS research is still in the exploratory stage, and several issues need to be addressed and determined: (1) Consistency of efficacy: Although some studies have shown that DTMS is effective in certain diseases, the results of these studies are variable and the effects are unpredictable. Further studies are needed to determine the consistency of efficacy and to identify patients who are best suited for this treatment modality; (2) Long-term safety and side effects: The long-term safety and potential side effects of DTMS are not fully understood, and although some studies have shown that the technique is relatively safe and well tolerated in the short term, the potential for adverse effects and potential risks associated with long-term use needs to be further evaluated; (3) Determining optimal stimulation parameters: DTMS involves the selection of stimulation site, stimulation frequency, stimulation intensity, and other parameters; it is unclear which stimulation parameters are most effective, and further research is needed to determine the optimal stimulation parameters and to ensure their consistency and reproducibility in clinical applications; (4) Disease-specific mechanism of action: The mechanism of action of DTMS on various diseases is not fully understood. A deeper understanding of its mechanism of action may help us to better understand and optimize its clinical application; and (5) Development of individualized therapeutic strategies: Since each patient's situation is unique, there is a need to develop methods for individualized therapeutic strategies that can better guide treatment and improve treatment efficacy by combining information from brain imaging technology and biomarkers. Addressing and identifying these issues will advance the use of DTMS in clinical practice and provide more effective options for the treatment of psychiatric and neurological disorders.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Hippocampus protection from apoptosis by Baicalin in a LiCl-pilocarpine-induced rat status epilepticus model through autophagy activation

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Abstract

BACKGROUND

Autophagy is associated with hippocampal injury following status epilepticus (SE) and is considered a potential therapeutic mechanism. Baicalin, an emerging multitherapeutic drug, has shown neuroprotective effects in patients with nervous system diseases due to its antioxidant properties.

AIM

To investigate the potential role of autophagy in LiCl-pilocarpine-induced SE.

METHODS

The drugs were administered 30 min before SE. Nissl staining showed that Baicalin attenuated hippocampal injury and reduced neuronal death in the hippocampus. Western blotting and terminal deoxynucleotidyl transferase dUTP nick end labeling assay confirmed that Baicalin reversed the expression intensity of cleaved caspase-3 and apoptosis in hippocampal CA1 following SE. Furthermore, western blotting and immunofluorescence staining were used to measure the expression of autophagy markers (p62/SQSTM1, Beclin 1, and LC3) and apoptotic pathway markers (cleaved caspase-3 and Bcl-2).

RESULTS

Baicalin significantly upregulated autophagic activity and downregulated mitochondrial apoptotic pathway markers. Conversely, 3-methyladenine, a

commonly used autophagy inhibitor, was simultaneously administered to inhibit the Baicalin-induced autophagy, abrogating the protective effect of Baicalin on the mitochondrial apoptotic level.

CONCLUSION
We illustrated that Baicalin-induced activation of autophagy alleviates apoptotic death and protects the hippocampus of SE rats.

Key Words: Baicalin; Status epilepticus; Autophagy; Mitochondrial apoptosis

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Core Tip: This study established the rat model of status epilepticus by intraperitoneally injecting LiCl-pilocarpine. Then, Baicalin was administered to the rats for treatment. The pathological changes of hippocampal were observed. Western blotting and terminal deoxynucleotidyl transferase dUTP nick end labeling assays were used to verify the inhibitory effect of Baicalin on apoptosis of rat hippocampal neuronal cells. We have drawn the conclusion that Baicalin protects the hippocampus from apoptosis.

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INTRODUCTION

It has been reported that 1% of the global population is affected by epilepsy, which has diverse etiologies and is characterized by recurrent and spontaneous seizures[1,2]. The most notable kind of epilepsy is temporal lobe epilepsy, characterized by a typical seizure that originates from the hippocampus-a structure located in the mesial temporal lobe[3-5]. Hippocampal injury following status epilepticus (SE) is due to oxidant damage. The accumulation of reactive oxygen species can harm hippocampal neurons, inducing cell death through an apoptotic or necrotic pathway, as hippocampal cells are highly sensitive to oxidative stress[6].

Autophagy is a highly conserved intracellular process that can be categorized into three classes: Macroautophagy, chaperone-mediated autophagy, and microautophagy. As the major type of autophagy, macroautophagy (hereinafter referred to as "autophagy") is crucial for eliminating cytoplasmic materials and maintaining intracellular homeostasis under pathological conditions[7,8]. This process of degrading long-lived proteins and cytoplasmic organelles is associated with SE, PD, and other neurodegenerative diseases[9]. Indications of autophagy variation have been observed in several neuroprotective drugs (*e.g.*, 17-allylamino-demethoxygeldanamycin and Tanshinone IIA), which simultaneously confirmed their ability to ameliorate SE-induced hippocampal neuronal death by upregulating autophagy[10,11]. Baicalin, as a natural extract, undergoes a safe and established preparation process and offers several significant advantages, including minimal side effects.

Baicalin-a traditional Chinese medicine-is among the main flavonoid compounds isolated from *Scutellaria baicalensis* Georgi and possesses multiple pharmacological properties, including neuroprotective[12], anti-inflammatory[13], antiapoptotic[14], and antioxidant[15] effects. Baicalin can freely cross the blood-brain barrier[14,16]; thus, it has been used to treat many nervous system diseases. Several studies have explored the relationship between autophagy and Baicalin. For example, Baicalin has been found to induce autophagy in tubercle bacillus-infected macrophages through the PI3K/Akt/mTOR signaling pathway, indicating its potential to alter disease progression by regulating autophagy activity[17]. Baicalin has also been shown to exert anticancer and anti-inflammatory effects by activating autophagy in pathogenic cells, such as human bladder cancer T24 cells, human hepatocellular carcinoma SMMC-7721 cells[18], and *Mycobacterium tuberculosis*-infected macrophages. A much-debated issue is whether Baicalin exerts neuroprotective effects while regulating autophagy. However, the mechanism by which Baicalin activates autophagy in the hippocampus following SE remains unclear. Thus, we aim to investigate the emerging role of autophagy in the hippocampus during SE and elucidate the precise mechanism underlying the neuroprotective effects of Baicalin.

MATERIALS AND METHODS

Animal preparation

Ninety-six pathogen-free Wistar rats (male, 180-220 g) were purchased from Shanghai Laboratory Animal Center. The rats were raised under controlled conditions with a 24 °C ± 1 °C temperature and a 12-h light/dark cycle. All rats had free access to water and food.

Rat model of SE and experimental groups

The rat model of SE was induced by intraperitoneally injecting adult Wistar rats with LiCl-pilocarpine[19]. The rats were lightly anesthetized through isoflurane inhalation and then intraperitoneally injected with 0.2 mL (127 mg/kg) of lithium chloride; Pilocarpine (30 mg/kg) was injected 16 h after LiCl administration. Rats that did not develop SE after the injection were excluded. The rats were randomly divided into four groups: Control, SE, SE + B100, and SE + B200 (Figure 1).

For the SE group, pilocarpine (25 mg/kg) was injected intraperitoneally 30 min after intraperitoneal injection of atropine methyl nitrate (2 mg/kg) to ameliorate peripheral cholinergic signs. The control group received a physiological salt solution instead of pilocarpine. The SE + B100 and SE + B200 groups were intraperitoneally injected with 100 mg/kg and 200 mg/kg of Baicalin, respectively, after the pilocarpine injection. The drug dosages used in this study were based on previous reports[20].

3-Methyladenine (3-MA) was used to inhibit autophagy. Subsequently, the rats were randomly divided into the following groups: Control, SE, SE + Baicalin, and SE + Baicalin + 3-MA. In the SE + Baicalin + 3-MA group, rats were injected with 400 nmoL 3-MA (2 μL) through an intracerebroventricular injection to the right lateral ventricle 1 h before SE induction, according to a previous study[21]. The SE + Baicalin and SE + Baicalin + 3-MA received a dose of 200 mg/kg of Baicalin. Isoflurane inhalation was used for anesthesia after SE induction. All rat brains were harvested for subsequent histological and biochemical studies.

Nissl staining

Twenty-four rats were executed 24 h after the onset of SE. HE staining was performed to detect damaged neurons in the hippocampus (six per group) based on a previous study[22]. Damaged neurons were characterized by an abnormal neuronal morphology, a dried-up cytoplasm with vacuoles, and a shrunken- hyperchromatic nucleus, as reported in a previous study[23].

Transferase dUTP nick end labeling staining

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining was conducted using an *in situ* cell death detection kit (Promega) to detect the cell apoptosis index. Briefly, rats were executed 24 h after the onset of SE, and 4-μm-thick coronal slices of the brain tissue were prepared using a paraffin slicer. Proteinase K (Nanjing Jianchen Co., Ltd.) was used to digest the coronal sections for 15 min. After deparaffinization, rehydration, and washing (with PBS), the sections were cultivated with a TdT reaction mix (Promega) containing TUNEL reaction fluid for 50 min at 37 °C (avoiding exposure to light from hereon). To stop the reaction, plastic coverslips were removed, and coronal slides were immersed in 2XSSC (Nanjing Jianchen Co., Ltd.) for 15 min. After three washes with 0.02 M TBS (5 min/wash), the liquid around the sections was dried, and the tablets were sealed with a seal containing DAPI fluorescent dye. Under a fluorescence microscope, localized apoptotic cells appeared green, and DAPI-stained nuclei appeared blue. Five slides per rat and five random fields per slide (scale bar = 50 μm) were selected to calculate the final average percentage and apoptosis index.

Western blotting

Hippocampal tissues were isolated, and hippocampus protein was extracted. The protein content was calculated using the BCA assay. Each quantity of protein per lane (30 μg) was separated on a 12% SDS-PAGE gel. The proteins were then electrotransferred onto a PVDF membrane (Millipore, United States). The membrane was blocked with 5% skim-fat milk prepared with TBST for 3 h. Primary antibody incubation was conducted with the following antibodies: LC3B (1:1000, Cell Signaling Technology), Beclin 1 (1:2000, Cell Signaling Technology), p62/SQSTM1 (1:500, Cell Signaling Technology), cleaved caspase-3 (1:500 dilution, Cell Signaling Technology), Bcl-2 (1:500 dilution, Cell Signaling Technology), and β-actin (1:2000, Bioworld Technology). Subsequently, secondary antibody incubation was conducted for 3 h at room temperature. The signals were visualized using an ECL reagent (Millipore), and band density was quantitatively analyzed using Quantity One software. The expression intensity was normalized to the loading control (β-actin).

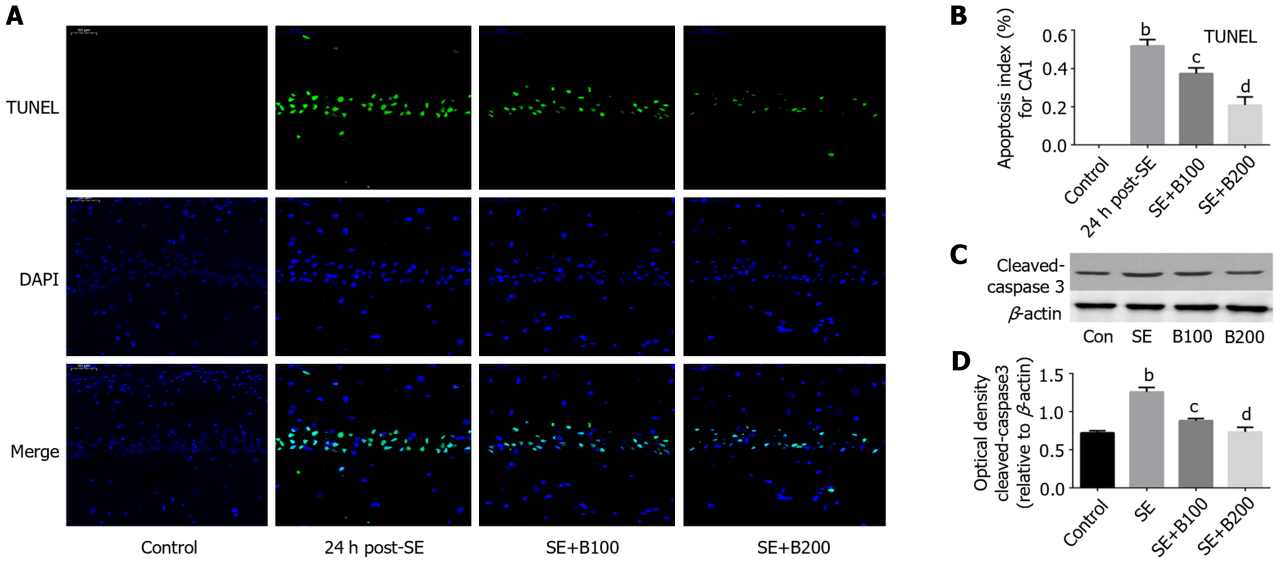
Immunofluorescent labeling

Immunofluorescence staining was performed to localize LC3 in the hippocampal cells. Brain sections from 24 rats (six per group) were prepared as described for the TUNEL staining procedure.

The slides were blocked with 5% normal donkey serum containing 0.01% Triton X-100 for 2 h. Primary antibody incubation was conducted with antibodies against LC3B (1:1000, Cell Signaling Technology) for 12 h at 4 °C. After washing three times with PBST, the sections were incubated with the secondary antibody (1:200, Alexa Fluor 594) for 2 h. DAPI treatment was applied for 1 min, and the sections were analyzed under a fluorescence microscope. We counted the cells with LC3 puncta, which appear as a result of LC3-II aggregation around the nucleus, and positive cells in the same field of view were quantified. In each coronal section, six fields (scale bar = 50 μm) around the hippocampus were randomly chosen to determine the average.

Statistical analysis

All results were represented as mean ± SD. The GraphPad Prism 6 software was used to analyze the data. Analysis of variance was used to compare data among multiple groups. Inspection level $\alpha = 0.05$ and $P < 0.05$ was considered a statistical difference.



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Figure 1 Baicalin ameliorated status epilepticus-induced neuronal apoptosis. A: Transferase dUTP nick end labeling staining was performed; B: Neuronal apoptosis was analyzed; C: Western blotting was performed; D: Semi-quantitative analysis of cleaved caspase-3 (n = 6). $^{b}P < 0.01$ compared to the control group; $^{c}P < 0.05$ and $^{d}P < 0.01$ compared to the status epilepticus group. Scale bar = 50 μm. SE: Status epilepticus; TUNEL: Transferase dUTP nick end labeling.

RESULTS

Baicalin exerted neuroprotective effects on the hippocampus following SE

Because the neurons in hippocampal CA1 are sensitive to SE stress, toluidine blue staining was performed to detect neuronal loss. The number of surviving neurons was significantly lower in the SE group than in the control group. However, Baicalin significantly increased the number of surviving neurons after SE (Table 1). To further confirm whether Baicalin provides neuroprotection to the hippocampus in SE rats, we monitored the latency of seizures following pilocarpine administration. The latent period (the time from pilocarpine administration to the onset of a seizure above the grade of Racine IV) was 29.60 ± 6.603 min in the SE group, whereas it was 41.70 ± 10.93 min and 63.80 ± 11.73 min in the Baicalin intervention groups (SE + B100 and SE + B200 groups, respectively). Treatment with different doses of Baicalin significantly prolonged the latency, and these differences were statistically significant ($P < 0.01$). The seizure latency in the SE + B200 group exceeded that in the SE + B100 group (Table 2). These results indicate that both concentrations of Baicalin exerted neuroprotective effects on the hippocampus dose-dependently. Therefore, the dosage of Baicalin (200 mg/kg) that produced superior effects was selected and employed for the subsequent experiments.

Baicalin reduced neuronal apoptosis in the hippocampus of SE rats

SE induced significant apoptosis of neurons in hippocampal CA1 ($P < 0.01$; Figure 1A and B). However, after 24 h, the apoptosis percentage was considerably lower in the SE + B100 and SE + B200 groups than in the SE group, with the SE + B200 group showing a more significant decrease (Figure 1B).

The level of pro-apoptotic cleaved caspase-3 in the SE + B200 group was significantly lower than in the SE group ($P < 0.01$; Figure 1C and D). These findings confirmed that Baicalin has neuroprotective effects against SE-induced apoptosis in an SE rat (Figure 2).

Baicalin upregulated autophagy in hippocampal neurons

To further investigate the potential relationship between autophagy and the neuroprotective effect of Baicalin, we measured three highly related autophagy proteins (p62/SQSTM1, Beclin 1, and LC3) as markers of autophagy using western blotting[24]. Under normal conditions, LC3 exists in a cytosolic form (LC3-I), whereas during autophagy activation, LC3-I is cleaved, lipidated, and inserted into autophagosome membranes as LC3-II. Beclin 1, located in the trans-Golgi network, contributes to autophagosome formation and localizes autophagy-related proteins in the pre-autophagosome membrane. p62, an important factor in cytoplasmic material delivery, is also degraded by autophagy and thus frequently serves as an autophagy marker.

As shown in Figure 3A-D, Beclin 1 and LC3-II levels were lower in the SE group than in the control group, whereas the level of p62 was significantly higher in the SE group. These results indicate that SE insults can partially inhibit autophagy activity. However, Baicalin treatment significantly upregulated the levels of Beclin 1 and LC3-II and downregulated the level of SQSTM1/p62 compared with the SE group, indicating that Baicalin activates autophagy in the pilocarpine-induced SE rat model. The results of immunofluorescence staining are consistent with those of western blotting (Figure 3). The SE group exhibited a slight decrease in the number of cells with LC3 puncta (Figure 4A). Moreover, Baicalin significantly enhanced the number of LC3-positive cells compared to the group SE (Figure 4B).

Table 1 Protective effect of Baicalin against neuron death in the hippocampal CA1 area following status epilepticus

Group	Neuron numbers (mean ± SD)
Control	129.0 ± 11.0
24 h post-SE	29.60 ± 6.603[a]
24 h post-SE + B100	41.70 ± 10.93[b]
24 h post-SE + B200	63.80 ± 11.73[c]

[a]$P < 0.01$ compared with the control group.
[b]$P < 0.01$ compared with the 24 h post-SE group.
[c]$P < 0.001$ compared with the 24 h post-SE group.
Data are represented as mean ± SD ($n = 6$). Under a light microscope, the surviving neurons showed regular cell morphology and round nuclei. Neuron number is expressed as the number of surviving neurons/0.5-mm-long hippocampal CA1 subfield. SE: Status epilepticus.

Table 2 Neuroprotective effect of Baicalin on seizure latency

Group	Seizure latency (mean ± SD), min
Control	
24 h post-SE	29.60 ± 6.603
24 h post-SE + B100	41.70 ± 10.93[a]
24 h post-SE + B200	63.80 ± 11.73[b]

[a]$P < 0.01$ compared with the 24 h post-status epilepticus (SE) group.
[b]$P < 0.001$ compared with the 24 h post-SE group.
Data are represented as mean ± SD ($n = 6$). SE: Status epilepticus.

Methyladenine inhibited the autophagy activated by Baicalin and abrogated its protective effect against the apoptotic pathway

To further explore the correlation between Baicalin-induced autophagy and apoptosis following SE, we applied 3-MA to detect alterations in autophagy proteins through western blotting. LC3-II and Beclin 1 levels were significantly lower in the SE + B + 3-MA group than in the SE + B group (Figure 3B and C). Conversely, the level of p62 was higher in the SE + B + 3-MA group than in the SE + B group (Figure 3D). These results indicate that normal baseline autophagy is possibly inhibited by SE and that Baicalin-induced autophagy is abolished by 3-MA.

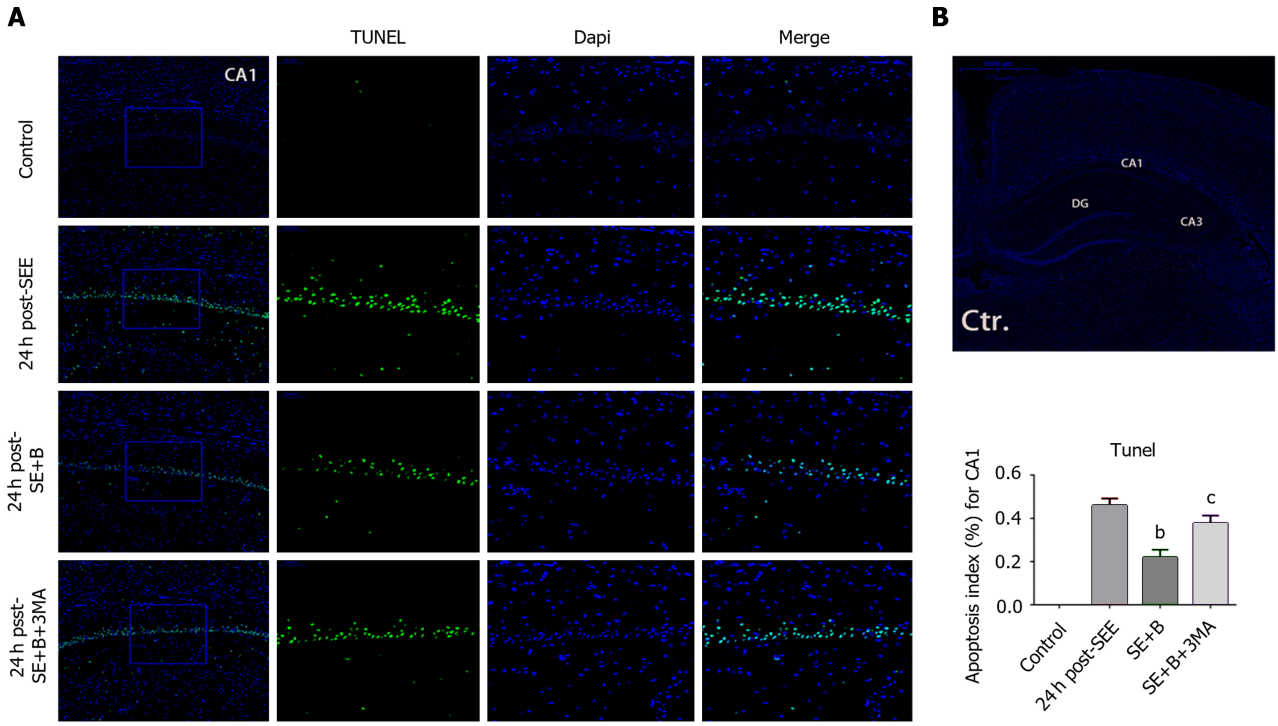
Activated caspase-3 degrades the substrate, and the degradation products enhance mitochondrial permeability, ultimately resulting in apoptosis. Bcl-2 can reportedly suppress apoptosis by inhibiting the activation of caspase-3, which is released in the upstream and downstream apoptotic pathways. To further investigate the mechanism underlying the neuroprotective effect of Baicalin following SE, we evaluated mitochondrial apoptosis–related proteins using western blotting (Figure 3E-G).

The level of Bcl-2 was lower in the SE group than in the control group, whereas the level of cleaved caspase-3 was significantly higher in the SE group than in the control group ($P < 0.01$; Figure 3E-G). Therefore, SE stress could induce neuronal apoptosis in the hippocampus, possibly through the regulation of mitochondrial apoptosis-related proteins. Furthermore, Baicalin restored Bcl-2 levels and reduced the level of cleaved caspase-3 compared with the SE group, suggesting that Baicalin ameliorated SE-induced mitochondrial apoptosis. In addition, 3-MA significantly increased mitochondrial apoptosis by enhancing cleaved caspase-3 and abrogating the restoration of Bcl-2 induced by Baicalin. Overall, these results illustrate that 3-MA exacerbated mitochondrial apoptosis in SE and abrogated the neuroprotective effect of Baicalin against the apoptotic pathway.

DISCUSSION

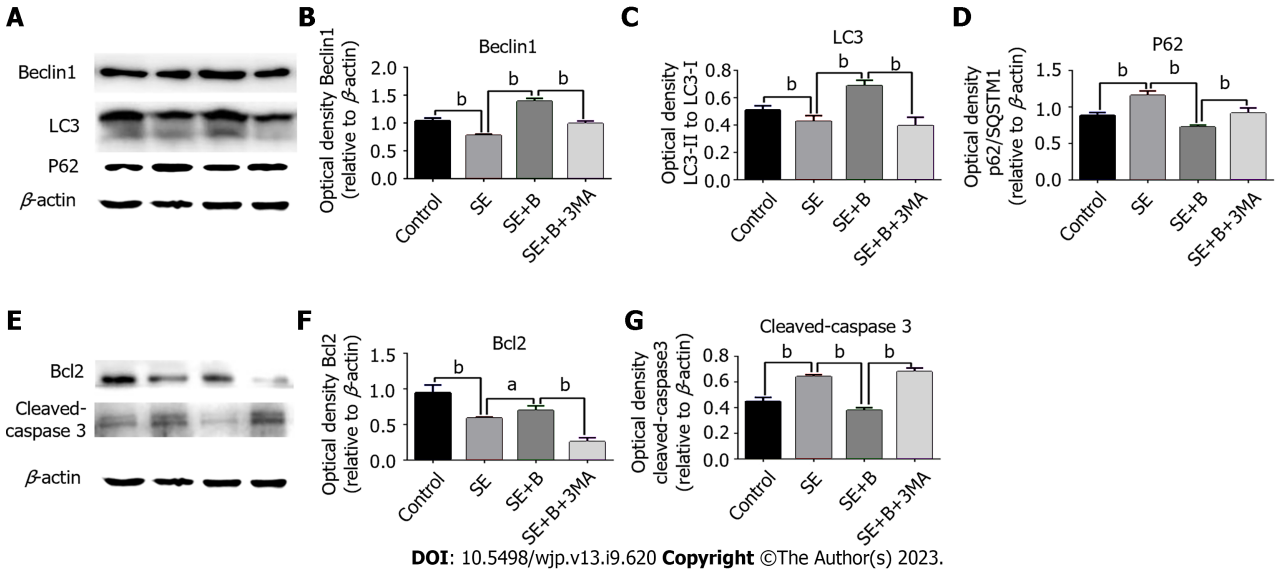
SE is a complex pathophysiological process involving multiple mechanisms. Baicalin is a traditional herbal medicine with multitarget protective effects against seizures[25]. A previous study in our laboratory found that Baicalin has a neuroprotective effect on the hippocampus following SE through the antiapoptotic pathway. However, the correlation between autophagy and the effects of Baicalin remained unclear.

To further investigate the function of Baicalin after SE, we monitored seizure latency and apoptosis in this study. The most significant finding (using western blotting and immunofluorescence) was that Baicalin promoted autophagy activity and inhibited mitochondrial apoptosis following SE. Furthermore, the intervention of 3-MA inhibited Baicalin-induced autophagy and even abolished its neuroprotective effects against mitochondrial apoptosis. These findings have



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Figure 2 Baicalin ameliorated status epilepticus-induced neuronal apoptosis. A: Transferase dUTP nick end labeling staining was performed; B: Neuronal apoptosis was analyzed. Baicalin protects the hippocampus from apoptosis following status epilepticus (SE), and 3-Methyladenine reverses Baicalin-induced neuroprotection in hippocampal neurons. Data are represented as mean ± SD. (n = 5), $^{b}P < 0.01$ *vs* the SE group; $^{c}P < 0.05$ *vs* the SE + B group. Scale bar = 50 μm. SE: Status epilepticus; TUNEL: Transferase dUTP nick end labeling; 3-MA: 3-Methyladenine.

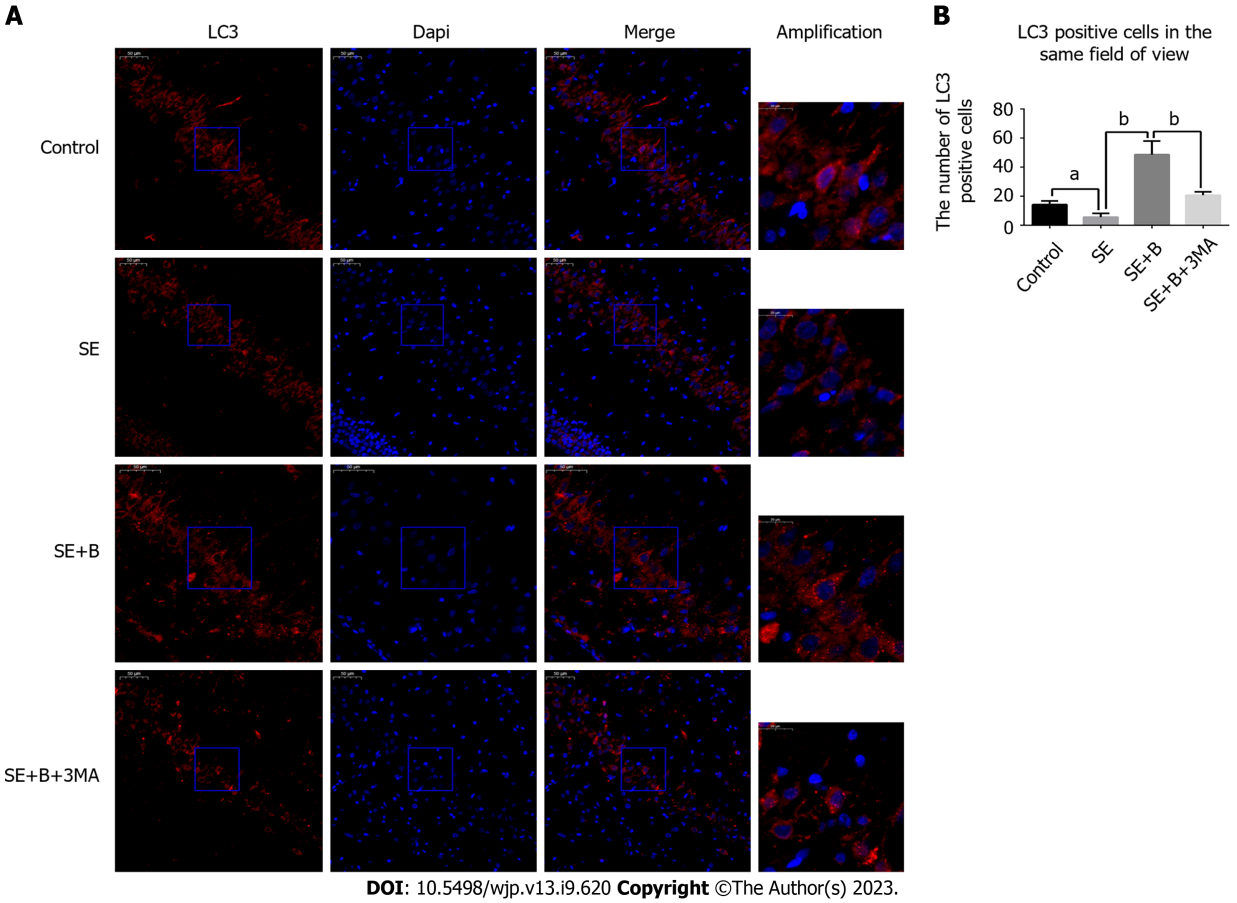


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Figure 3 The autophagy markers (p62/SQSTM1, Beclin 1, and LC3) and apoptotic pathway markers (cleaved caspase-3 and Bcl-2) were measured using western blotting. A: The autophagy markers (p62/SQSTM1, Beclin 1, and LC3) were measured using western blotting; B: The expressions of Beclin 1; C: The expressions of LC3; D: The expressions of p62; E: The apoptotic pathway markers (cleaved caspase-3 and Bcl-2) were measured using western blotting; F: The expressions of Bcl-2; G: Cleaved caspase-3 were analyzed. n = 6. $^{a}P < 0.05$ and $^{b}P < 0.01$. SE: Status epilepticus; 3-MA: 3-Methyladenine.

theoretical implications for the treatment of epilepsy by regulating autophagy.

In recent decades, the focus on alterations in autophagy after SE has increased due to the close relationship between autophagy activity and hippocampal injury. Different theories regarding the role of autophagy in nervous system diseases exist in the literature. The prevailing view is that activated autophagy has a protective role in rat models of ischemia-reperfusion[26-29], but there is still some ambiguity. A previous study focusing on autophagy has noted that autophagy dynamics in a rat's hippocampus act as determinants for epileptogenesis, suggesting that applying autophagy



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Figure 4 The number of LC3-II-positive neurons was partially decreased by SE and increased by Baicalin. 3-Methyladenine **reversed the Baicalin-induced alteration.** A: Representative immunofluorescence staining; B: Positive neuronal cells were analyzed. $n = 6$. $^{a}P < 0.05$ and $^{b}P < 0.01$ *vs* the relevant group. The number of LC3-II-positive cells/0.5-mm-long subfield of the hippocampus under a light microscope was regarded as the numerical value (scale bar = 50 μm). SE: Status epilepticus; 3-MA: 3-Methyladenine.

inducers such as rapamycin, an mTOR inhibitor, to activate autophagy has an unambiguous effect on severe epileptic seizures[30,31]. Similarly, several studies have supported the view that activating autophagy through specific factors could provide neuroprotection in rat models of epilepsy[32], suggesting that autophagy induction plays a positive role in cell survival.

One significant finding is the activation of autophagy using recombinant human erythropoietin, which has been recently confirmed to exert neuroprotective effects and help ameliorate apoptosis in hippocampal neurons after SE[33]. In our study, we showed that Baicalin treatment significantly upregulated autophagy activity based on alterations in autophagy-related proteins and immunofluorescence staining of LC3-II puncta. In addition, decreased neuronal apoptosis and prolonged seizure latency were observed in Baicalin-treated groups, consistent with the findings of previous studies that support the neuroprotective effect of autophagy on the hippocampus in patients with seizures. A prior report concluded that impaired autophagy possibly contributes to epileptogenesis, which may be interesting as a potential therapeutic target for treating and preventing epilepsy[34]. Nevertheless, we could not elucidate whether autophagy inhibition promotes the occurrence of epilepsy, which is a limitation of our study.

There are possible situations where autophagy plays a dual role in epilepsy. The practical effect of autophagy depends on the degree of its activation due to the release of various deleterious factors following SE. The possible situations are as follows: (1) Inhibited autophagy potentially contributing to epileptogenesis, although a definitive causal relationship between autophagy and epileptogenesis in rat models has not been established; (2) Proper activation of autophagy benefiting the survival of hippocampal neurons by generating adenosine triphosphate; and (3) SE causing autophagic death and apoptosis in hippocampal neurons due to excessive autophagy[35].

It has not been determined whether administering neuroprotective drugs increases or decreases autophagic flow. For instance, we can only detect signs of decreased autophagy because the activation of autophagy promotes the clearance of autophagosome accumulation[36]. However, the amelioration of apoptosis by autophagy activation in epilepsy is complex and has not been fully elucidated.

Pro-apoptotic materials, such as damaged mitochondria and Bax accumulation induced by traumatic brain injury, can be eliminated by increased autophagy flux[37].

A previous study reported another possible mechanism involving autophagy activation and sequestration of abnormal proteins that trigger endoplasmic reticulum (ER) stress[38]. Hence, autophagy activation may inhibit ER stress in response to external stimuli and ameliorate apoptosis[39]. However, the role of autophagy in apoptosis after SE remains

unknown.

In this study, we discovered that Baicalin induces autophagy activation and alleviates apoptosis in hippocampal neurons following SE. Significantly, the abolition of Baicalin-induced autophagy and its neuroprotective effects against the mitochondrial apoptotic pathway by 3-MA administration suggest that autophagy activation may reduce neuronal apoptosis by removing damaged mitochondria after SE.

These results further support previous studies that have linked mitophagy, apoptosis, and neuron survival[34] and reported that mitophagy exerts anti-apoptosis effects, which promote cell survival. In this research, only male rats were used to reduce the impact of gender differences on research results. However, further experiments need to be validated with female animals.

CONCLUSION

In conclusion, we demonstrated that Baicalin prolongs seizure latency, ameliorates hippocampal injury, increases the survival rate of hippocampal neurons, and reduces mitochondrial apoptosis following SE in rats through autophagy activation. This study contributes to the pharmacological effects of traditional Chinese herbs such as Baicalin. Furthermore, it provides a new way of regulating autophagy for treating SE.

ARTICLE HIGHLIGHTS

Research background

Autophagy is associated with hippocampal injury after status epilepticus (SE), and is considered a potential mechanism with curative value. Baicalin, an emerging multi-therapeutic drug that has been demonstrated to exert neuroprotective effects in patients with nervous system diseases because of its antioxidant property.

Research motivation

We investigate the influence of Baicalin on the improvement of LiCl-Pilocarpine-induced rat SE.

Research objectives

We intended to investigate the potential role of autophagy in LiCl-pilocarpine-induced SE.

Research methods

Nissl staining showed that Baicalin attenuates hippocampal injury and reduces the number of neuronal deaths in the hippocampus. Besides, the expression intensity of cleaved caspase-3 and apoptosis in hippocampal CA1 following SE were reversed by Baicalin, as proven by western blotting and terminal deoxynucleotidyl transferase dUTP nick end labelling assay. Furthermore, western blotting and immunofluorescence staining were used to measure the expression of autophagy markers (p62/SQSTM1, Beclin 1, and LC3) and apoptotic pathway markers (cleaved caspase-3 and Bcl-2).

Research results

Baicalin significantly upregulated autophagic activity and downregulated mitochondrial apoptotic pathway markers. Conversely, 3-methyladenine, a commonly used inhibitor of autophagy, was simultaneously administered to inhibit the autophagy induced by Baicalin, abrogating the latter's protection on the mitochondria apoptotic level.

Research conclusions

We illustrated that Baicalin induced activation of autophagy alleviates apoptotic death and protects the hippocampus of SE rats.

Research perspectives

The improvement of LiCl-Pilocarpine-induced rat SE by Baicalin was validated.

FOOTNOTES

Author contributions: Yang B and Wen HY contributed equally to this work; Yang B and Wen HY proposed the overall research goal and designed the research plan and model design; Yang B, Wen HY, Liang RS, and Lu TM conducted feasibility analysis, review, and supervision of the experiment; Yang B, Wen HY, Zhu ZY, and Wang CH conducted statistical processing and analysis of the data; Yang B and Wen HY are responsible for writing the first draft of the paper; Yang B, Wen HY, and Liang RS were responsible for the review, revision, and quality control of the paper; all authors determined the final draft of the paper.

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ORIGINAL ARTICLE

Basic Study

Exosomal miR-320e through wnt2targeted inhibition of the Wnt/β-catenin pathway allevisate cerebral small vessel disease and cognitive impairment

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Abstract

BACKGROUND

Exosomal miRNAs play crucial roles in many central nervous system diseases. Cerebral small vessel disease (CVSD) is a small vessel disease that is affected by various factors. This study aimed to investigate the role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and assess its clinical correlation with psychiatric symptoms in patients with CVSD.

AIM

To explore whether exosomal miR-320e could suppress the Wnt/β-catenin pathway and play a protective role in CVSD progression, as well as examine its potential correlation with cognitive impairment and depression in patients with CVSD.

METHODS

Differentially expressed exosomal miRNAs were filtered by sequencing plasma exosomes from patients with CVSD and healthy controls. Bioinformatics and dual luciferase analyses were used to confirm the binding of miR-320e to Wnt2, and the mRNA and protein levels of downstream components in the Wnt/β-catenin pathway were evaluated when overexpressed or with knockdown of miR-320e under H_2O_2-induced oxidative stress. In addition, Wnt2-targeting siRNA was used to confirm the role of miR-320e in the Wnt2-mediated inhibition of the Wnt/β-catenin pathway. A retrospective analysis was conducted among patients with CVSD to confirm the correlation between miR-320e expression and the severity of cognitive impairment and depression, which were quantified using the Montreal

Cognitive Assessment (MoCA)/Executive Function Assessment (EFA), and the Hamilton Depression Scale (HAMD)/Beck Depression Inventory (BDI), respectively.

RESULTS

High-throughput sequencing revealed that exosomal miR-320e was downregulated in patients with CVSD. Bioinformatics analysis and dual-luciferase reporter gene experiments showed that exosomal miR-320e inhibited the Wnt/β-catenin pathway in response to oxidative stress by targeting the 3' noncoding region of Wnt2. Uptake of exosomes carrying miR-320e into endothelial cells could also target Wnt2 and inhibit the Wnt2/β-catenin pathway. Elevated miR-320e expression may protect patients with CVSD from relatively severe cognitive impairment and depression, as it was found to have a positive correlation with the MoCA/EFA and HAMD/BDI scores.

CONCLUSION

Our results suggest that exosomal miR-320e suppresses the Wnt/β-catenin pathway and may play a protective role in CVSD progression.

Key Words: Exosome; Cerebral small vessel disease; miRNA-320e; Wnt2; Wnt/β-catenin pathway; Depressed

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Core Tip: Exosomal miR-320e is downregulated in patients with cerebral small vessel disease (CVSD), and it inhibits the Wnt/β-catenin pathway by targeting Wnt2 in response to oxidative stress. Uptake of exosomes carrying miR-320e can also target Wnt2 and inhibit the Wnt2/β-catenin pathway. Elevated miR-320e expression may protect patients with CVSD from severe cognitive impairment and depression, as it correlates positively with Montreal Cognitive Assessment/Executive Function Assessment and Hamilton Depression Scale/Beck Depression Inventory scores. Therefore, exosomal miR-320e may play a protective role in CVSD progression by suppressing the Wnt/β-catenin pathway, indicating its potential as a therapeutic target for CVSD.

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INTRODUCTION

Stroke is the deadliest disease in China and the second most disabling disease worldwide, and its socioeconomic burden has increased dramatically in the last three decades[1]. Cerebral small vessel disease (CVSD) accounts for 20%–30% of ischemic stroke cases. CVSD is a series of clinical, imaging, and pathological syndromes caused by various etiologies that affect the small arteries, microarteries, capillaries, microvenules, and small veins in the brain[2]. White matter and deep gray matter damage caused by CVSD is also considered a major cause of cognitive impairment due to damaged crosstalk between the arteries, capillaries, and small veins[3]. Currently, conventional anti-hypertensive, lipid regulatory, and antiplatelet aggregation treatments are not effective in improving cognitive and motor function impairments in patients [4,5]. Thus, new therapeutic targets or mechanisms for CVSD are warranted.

Exosomes, presenting as 30-150 nm extracellular vesicles in diameter, carry rich contents to exert their bioinformatics function near or distantly[6-8] and have been demonstrated to play important roles in vascular diseases, such as atherosclerosis, diabetic vasculopathy, and stroke[9-11]. Moreover, miRNAs (a class of 17–24 nt small, noncoding RNAs) have been identified in exosomes and are involved in the biogenesis, release, and uptake of relevant proteins by mediating post-transcriptional gene silencing by binding to target mRNAs[12]. Exosomal miRNAs participate in numerous biological processes during nerve injuries. Exosomal miR-451a plays a protective role against cerebral ischemia/reperfusion injury[13]. Exosomal miR-124a can be transported to glioblastomas to play a tumor-suppressive role[14]. Therefore, in this study we performed high-throughput sequencing analysis of plasma exosomal miRNAs between patients with CVSD and healthy controls and found that exosomal miR-320e, with the most significant difference, was speculated to be a highly promising target relevant to CVSD pathogenesis.

With aging and the presence of other risk factors, the integrity of the vasculature is gradually lost. This affects various cellular pathways, including the Wnt/β-catenin pathway, which is known to regulate vascular neogenesis, vascular remodeling, and blood-brain barrier maturation in response to harmful stimuli[15,16]. The Wnt family of proteins has been reported to play essential roles in the development of the nervous system[17]. miRNAs have been found to regulate vascular function by targeting the Wnt pathway, as evidenced by the involvement of miR-29b in vascular smooth muscle calcification[18] and the regulation of miR-330 in the process of unstable atherosclerotic plaque formation and vascular endothelial cell proliferation[19]. These studies indicate that the inhibition of the Wnt/β-catenin pathway may delay the progression of some diseases, such as cancer[20], axonal degeneration[21], and chronic kidney disease[22]. However, the

mechanism by which exosomal miR-320e regulates the Wnt/β-catenin pathway in cerebrovascular disease has not yet been explored.

Among the secretory glycoproteins belonging to the Wnt family, Wnt2 shows potent antidepressant effects and can inhibit the development of depressive disorders, suggesting the direct binding of miR320e to Wnt2[23]. In this study, we assessed the regulatory effects of miRNA-320e on the Wnt/β-catenin pathway by targeting Wnt2 in endothelial cells under oxidative stress. Furthermore, the predictive value of decreased exosomal-derived miR-320e for the clinical deterioration of depression and impaired cognition in CVSD was analyzed in a retrospective study.

MATERIALS AND METHODS

Sequencing of exosomal microRNAs from patients with CVSD

In total, 120 blood samples were collected from patients with CVSD and healthy subjects at the Qingdao University Affiliated Hospital between January 2017 and January 2019 (80 patients with CVSD and 40 controls). Baseline information of the patients with CVSD and controls was shown in the Supplementary Material. The inclusion criteria were based on the STRIVE diagnostic criteria, with the following: (1) Magnetic resonance imaging (MRI) manifestations, including lacunar infarctions, white matter lesions, cerebral microbleeds, and perivascular space enlargement > 2 mm and brain atrophy; (2) Clinical symptoms such as dizziness, fatigue, and cognitive changes; and (3) Age > 18 years. Patients with a definite diagnosis of cardiovascular or cerebrovascular diseases, severe head and neck artery stenosis, arteriosclerosis, incomplete brain MRI, blood system diseases or tumors, or severe liver and kidney insufficiencies were excluded. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. All specimens were collected after obtaining authorization from the patients and their families and signing a consent form.

Isolation and extraction of exosomes

Thermo Fisher Scientific's Total Exosome Precipitation Reagent (from plasma) kit (REF4484451; Waltham, Massachusetts, United States Thermo Fisher Scientific) was used to extract the exosomes. Although ultracentrifugation was often noted for the ability to produce highly purified exosome, filtration could more conveniently generate a higher yield. However, both filtration and ultracentrifugation methods had their unique advantages and were well accepted in the area of exosome extraction.

The frozen plasma was thawed at room temperature, and 200 μL was placed in an EP tube and centrifuged at 2000 × g for 20 min at room temperature. The supernatant was collected in a new EP tube at room temperature and centrifuged again at 10000 × g for 20 min. Then, 100 μL of Phosphate-buffered saline (PBS) was added to the resulting supernatant and vortexed. Then, 10 microliters of proteinase K (Thermo Fisher Scientific 4485229) was added, shaken well and incubated at 37 °C for 10 min. Then, 60 microliters of extraction reagent was added to the incubated liquid, fully vortexed until turbid, and incubated at 4 °C for 30 min. Next, the sample was removed from the 4 °C environment and centrifuged it at 10000 × g for 5 min at room temperature. A pale yellow or colorless precipitate was observed, and the supernatant was discarded. Finally, we resuspended the sample in 100 μL of PBS to obtain an exosome solution and proceeded to the next step immediately or stored it at -80 °C.

Identification of exosomes

The morphology of the exosomes was observed by transmission electron microscopy, and the quality of the isolated exosomes was determined by nanoparticle tracking analysis. Exosome surface proteins were examined using western blotting.

Extraction of exosomal RNA

Total RNA was extracted using the miRNeasy Serum/Plasma Kit (50) (Cat. No. 217184). Immediately or after thawing the cryopreserved exosome solution, we took 100 microliters for lysis with 500 microliters of TRIzol and incubated at room temperature for 5 min. After addition of 100 μL of chloroform, the sample was vortexed and incubated at room temperature for 3 min. The samples were centrifuged at 12000 × g for 15 min at 4 °C. We transferred the upper part of the aqueous phase after centrifugation into a new EP tube, added absolute ethanol, mixed well, transferred to a spin column, centrifuged at 8000 × g for 15 s, and discarded the filtrate. Then, we added 700 microliters of RWT to the spin column at room temperature, centrifuged at 8000 × g for 15 s, and discarded the filtrate; added 500 microliters of RPE to the spin column at room temperature, centrifuged at 8000xg for 15 s, and discarded the filtrate; added 500 microliters of 80% ethanol, centrifuged the spin column at room temperature at 8000 × g for 2 min, changed the spin column into a new EP tube, and centrifuged at 12000 × g for 5 min for drying. Finally, 14 μL of enzyme-free water was added, and approximately 14 μL of total RNA was obtained by centrifugation at 12000 × g for 1 min after 1 min.

Cell culture

Human umbilical vein endothelial cells (HUVECs), cell models with stem cell potential commonly used for vascular endothelial cell experiments, were cultured in 90% dulbecco's modified eagle medium (DMEM) containing 10% FBS and 1.5% penicillin-streptomycin. All cells were cultured in 5% CO_2 at 37 °C in a humidified atmosphere. DMEM, FBS, and penicillin-streptomycin were purchased from BI (BI, United States), and trypsin was purchased from Thermo Scientific. Oxidative stress stimulation was induced using a 1 mmol/L solution of DEME prepared with hydrogen peroxide for 30 min. R-Spondin-1 (the Wnt pathway agonist) and WIF1 (the Wnt pathway inhibitor) were procured from MCE (MCE,

United States) using complete medium diluted to 60 and 20 ng/mL, respectively, for 24 h of cell culture before subsequent treatment as needed. The plasmids of wild-type and mutated Wnt2 3'-UTR and Wnt2-targeting siRNA, as well as the miR-320e mimic and inhibitor required for the transfection of HUVECs, were constructed by Gikai Gene (Shanghai Genechem Co, Ltd.).

Plasma membrane staining

We used a DiI (DiI perchlorate, C59H97CIN2O4) cell membrane orange-red fluorescent probe to stain the cell and exosome membranes (Yeasen; 40726ES10, China), and absorbance was detected at 550/567 nm.

Western-Blot analysis for protein expression detection

Cell lysis buffer (Elabscience Biotechnology Co., Ltd., China) for western blotting was used for total protein extraction. Following centrifugation at 4 °C (12000 × g, 15 min), a BCA kit (Elabscience, China) was used to quantify the protein concentrations. Protein samples were separated using polyacrylamide gel electrophoresis and transferred onto membranes (ACE Biotechnology, China). Freshly prepared Tris-buffered saline (TBS) containing 5% nonfat milk was used to block the membranes for 2 h at room temperature. The blots were probed with primary antibodies at 4 °C overnight at a dilution ratio of 1:1000. The primary antibodies used for the detection of Wnt/β-catenin pathway by western blotting were as follows: Wnt2, FZD2, Axin2, GSK3β, and β-catenin (Proteintech Group, Inc, United States). Membranes coated with primary antibodies were washed three times with TBS-0.05% Tween 20, followed by incubation at room temperature with the corresponding secondary antibodies for 1 h. The blots were then incubated in the dark with ECL and visualized by exposure to enhanced chemiluminescence reagents (GE Healthcare, United States). ImageJ software 1.4.3.67 (National Institutes of Health, United States) was used to analyze the grey scale values of the blots.

Detection of gene expression with real-time PCR

Total RNA was isolated from the cells using TRIzol Reagent (Invitrogen, United States). Goldenstar RT6 cDNA Synthesis Kit Ver. 2 (TSINGKE, China) was used to synthesize cDNA from the RNA. Wnt2, FZD2, Axin2, GSK3β, and β-catenin were detected by a 2xT5 Fast real-time polymerase chain reaction (PCR) Mix (SYBR Green I) kit (TSINGKE, China). Primer design and synthesis were performed by the Sangon Corporation (Shanghai, China), and the primer sequences were listed in the Supplementary Material. The results of RT-PCR analysis were calculated by the − ΔΔCt method.

Retrospective clinical study in patients with CVSD

Patients and Ethics: Using a retrospective analysis, relevant information on patients with CVSD who met the inclusion criteria was collected between January 2022 and December 2022 at the Department of Neurology of Qingdao University Affiliated Hospital. The inclusion criteria were as follows: (1) Aged–50-80 years; (2) Meeting the diagnostic criteria for CVSD according to the Expert Consensus on Diagnosis and Treatment of CVSD in China (2021); and (3) Agreement to participate in this study and signed an informed consent form. The exclusion criteria were as follows: (1) Other neurological or psychiatric diseases affecting cognitive function; (2) Other systemic diseases or medication history affecting vascular function; and (3) Other factors affecting exosome isolation or detection. Healthy volunteers who underwent physical examinations at the health examination center during the same period were enrolled as controls after obtaining informed consent and met the following conditions: (1) No clinical symptoms or signs; (2) No abnormal laboratory or imaging examinations; and (3) No history of chronic diseases or medication use. This study was approved by the ethics committee of our hospital. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Treatments: Standard therapies were provided to patients with CVSD after a comprehensive assessment of their condition. Doctors developed a personalized treatment plan targeting the risk factors for CSVD in each patient, including anti-hypertensive drugs (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, or β-receptor blockers), antiplatelet drugs (such as aspirin, clopidogrel, or ticagrelor), anticoagulation drugs (such as warfarin, dabigatran etexilate, or rivaroxaban), lipid-lowering therapy (such as simvastatin and atorvastatin), and diabetes controlling drugs (such as insulin and metformin). In addition, lifestyle improvements, such as quitting smoking, limiting alcohol intake, maintaining a healthy diet, and engaging in appropriate exercise, were recommended. For cognitive dysfunction related to CVSD, cholinesterase inhibitors and memantine were chosen to improve depression, anxiety, apathy, and psychiatric symptoms.

Psychiatric Assessments: The following assessment scores of patients were collected: (1) Cognitive function assessment, including the Montreal Cognitive Assessment (MoCA) and the Executive Function Assessment (EFA); and (2) Depression symptom assessment, including the Hamilton Depression Scale (HAMD) and the Beck Depression Inventory (BDI). Utilizing the average scores that patients received as the cutoff point, the CVSD population in this study was divided into two groups: Relatively more severe and relatively better disease.

Statistical analysis

Statistical analysis was performed using SPSS 26.0. Quantitative data were presented as the mean ± SD and were compared using the Wilcoxon test between the two groups, while categorical data were expressed as frequencies (percentages). For western blotting, the mean normalized gray level in the control group was defined as a relative FC of 1. For qRT-PCR, all data were normalized to the FC of the control group. Correlation analysis was performed using the Spearman's rank correlation coefficient. Statistical significance was set at $P < 0.05$. The statistical method of this study was reviewed by Ai-Jun Ma from Qingdao University Affiliated Hospital.

RESULTS

Identification of the miRNA expression profiles in CVSD patients

The results of the identification of the extracted exosomes were shown in Supplementary Material. In total, 120 blood samples were collected from 80 patients with CVSD and 40 healthy controls. The expression of miRNAs in plasma exosomes from patients with CVSD and healthy controls was detected by high-throughput detection. As shown in Figure 1A, the results showed that the expression of 38 miRNAs was significantly different in the plasma exosomes of patients with CVSD compared with the controls. Among these differentially expressed miRNAs, 18 miRNAs were significantly upregulated and 20 miRNAs were downregulated. A heatmap of the miRNAs with significant differential expression was shown in Figure 1B. Next, miR320e, miR-498, miR-6776, and miR-455 were verified using real-time PCR. This trend in the real-time PCR results was consistent with that of the miRNA sequencing results. Previous studies have shown that miR-320 regulates the biological behavior of ischemic neurons and changes the state of tissue inflammation and oxidative stress through drug regulation[24,25]. miR-320e was significantly downregulated compared with that in the healthy control group (16.8478, 95%CI = 7.4456–26.2501), and the difference was statistically significant ($P < 0.001$) (Supplementary Material), indicating that this molecule might play an important role in the pathophysiological process of CVSD.

MiR-320e targets the Wnt2 gene and exerts post-transcriptional regulation

According to the RNACentral and TargetScan human databases, Wnt2 was one of the target mRNAs of miR-320e. In addition, functional enrichment analysis showed that miR-320e was involved in the regulation of cellular responses to stress, mRNA metabolic processes, cell division, and apoptosis (Figure 1C), which was associated with vascular endothelial structural integrity. In contrast to other differentially expressed miRNAs, miR-320e and its target gene Wnt2 were associated with both leukocyte transendothelial function and vascular structural integrity, leading us to speculate that miR-320e may play an important role in the progression of CVSD development.

To verify the binding relationship between miR-320e and Wnt2, we performed a dual-luciferase reporter assay. The plasmids of wild-type and mutated Wnt2 3′-UTR were constructed and cotransfected with overexpressed miR-320e and control mimics. The results showed that the fluorescence intensity in the WT-Wnt2/miR320e-overexpressed group was significantly reduced (Figure 2A and B), indicating that miR320e specifically bound to Wnt2. A two-factor recovery experiment was conducted to prevent off-target effects. The results showed that the protein expression of Wnt2, Axin2, β-catenin, FZD2, and GSK3β was downregulated in the group that was transfected with the miR-320e mimic. In contrast, the endothelial cells transfected with the inhibitors targeting miR-320e showed higher expression of Wnt2, Axin2, β-catenin, FZD and GSK3β than those in the control group (Figure 2C and D). The fluorescence photos observed after transfection of miR-320e mimic and inhibitor were shown in Figure 2E. These results indicated that miR-320e inhibited the expression of Wnt2 at the post-transcriptional level as well as the activation of downstream β-catenin pathways.

The Wnt/β-catenin pathway was involved in the H_2O_2-induced oxidative stress response

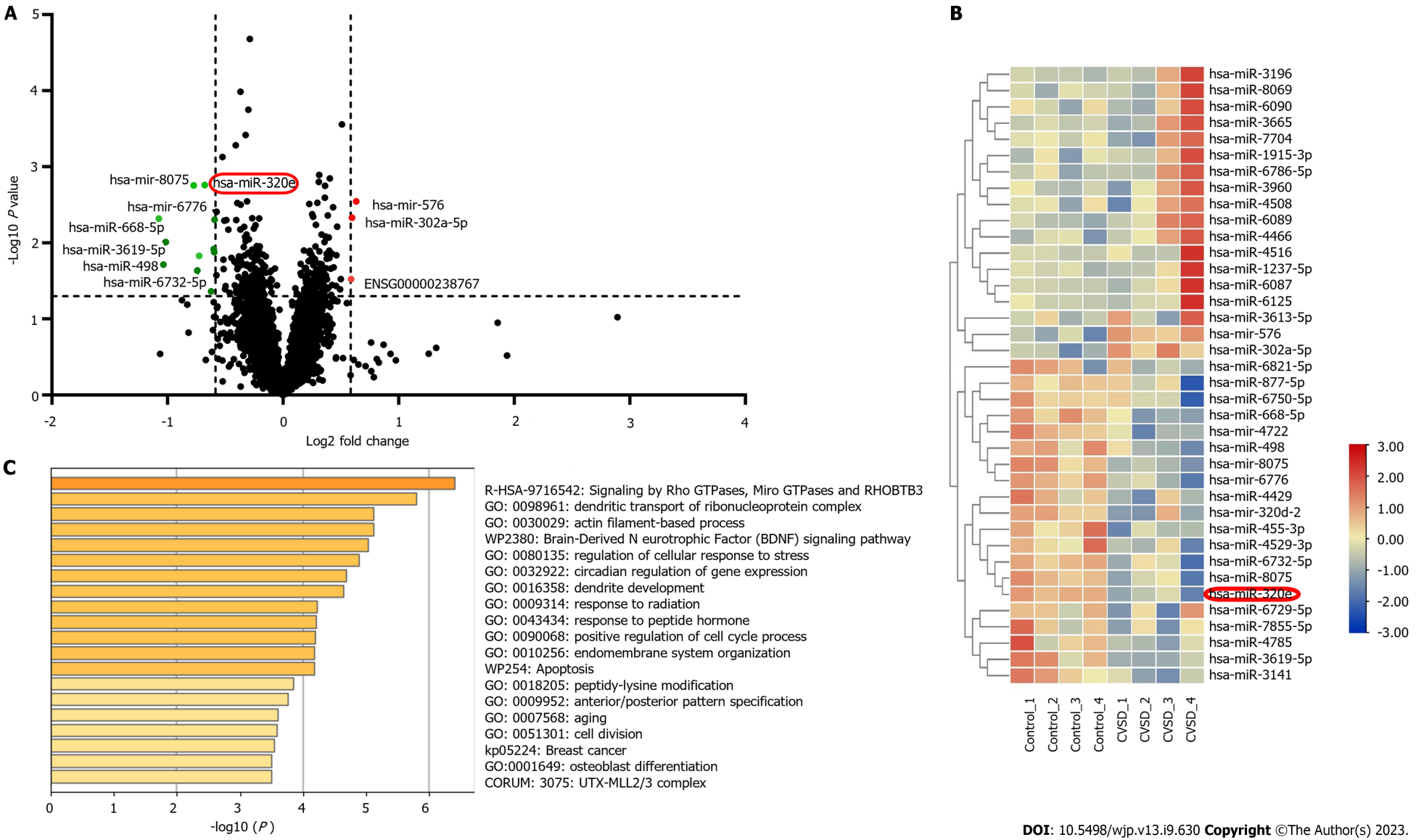
HUVECs were treated by adding H_2O_2 to the medium to create oxidative stress in the cell culture environment. The expression levels of Wnt2, FZD2, Axin2, GSK3β and total β-catenin in the Wnt/β-catenin pathway were all increased (Figure 3A-C). Oxidized HUVECs were further stimulated with the Wnt pathway inhibitor WIF1 or the agonist R-spondin in parallel with the mock control. We found that the protein expression of Wnt2, FZD2, Axin2, GSK3β and total β-catenin in the WIF1 + H_2O_2-treated group was similar to that in the WIF1-treated group without oxidative stress, meaning the Wnt2 inhibitor effectively alleviated the H_2O_2-induced Wnt/β-catenin pathway (Figure 3D-G). Meanwhile, R-spondin activated the Wnt2-mediated β-catenin pathway, and the expression of downstream components in the R-spondin + H_2O_2 group was enhanced compared to that in the group treated with R-spondin alone (Figure 3D and F-H). The above data indicate that the Wnt/βcatenin pathway and its relevant components were upregulated under H_2O_2-induced oxidative stress.

miR-320e inhibited the H_2O_2-induced Wnt/β-catenin pathway through targeting Wnt2

To demonstrate the effects of transfection, we used plasmids or siRNAs with green fluorescent labels and puromycin resistance. The fluorescence images observed after transfection of miR-320e mimics, mimic control, Wnt2-targeting siRNA, and siRNA control were shown in Figure 4A and B. Utilizing H_2O_2–treated HUVECs, when signaling in the Wnt/β-catenin pathway including Wnt2 was obviously inhibited by miR-320e mimics compared with control mimics, Wnt2-targeting silencing but not the siRNA control reversed the inhibition of the Wnt/β-catenin pathway (Figure 4C). Protein and mRNA expression detected by western blotting and real-time PCR showed similar results under H_2O_2-induced oxidative stress (Figure 4D-G). These data show that miR-320e inhibited the H_2O_2–induced Wnt/β-catenin pathway by targeting Wnt2.

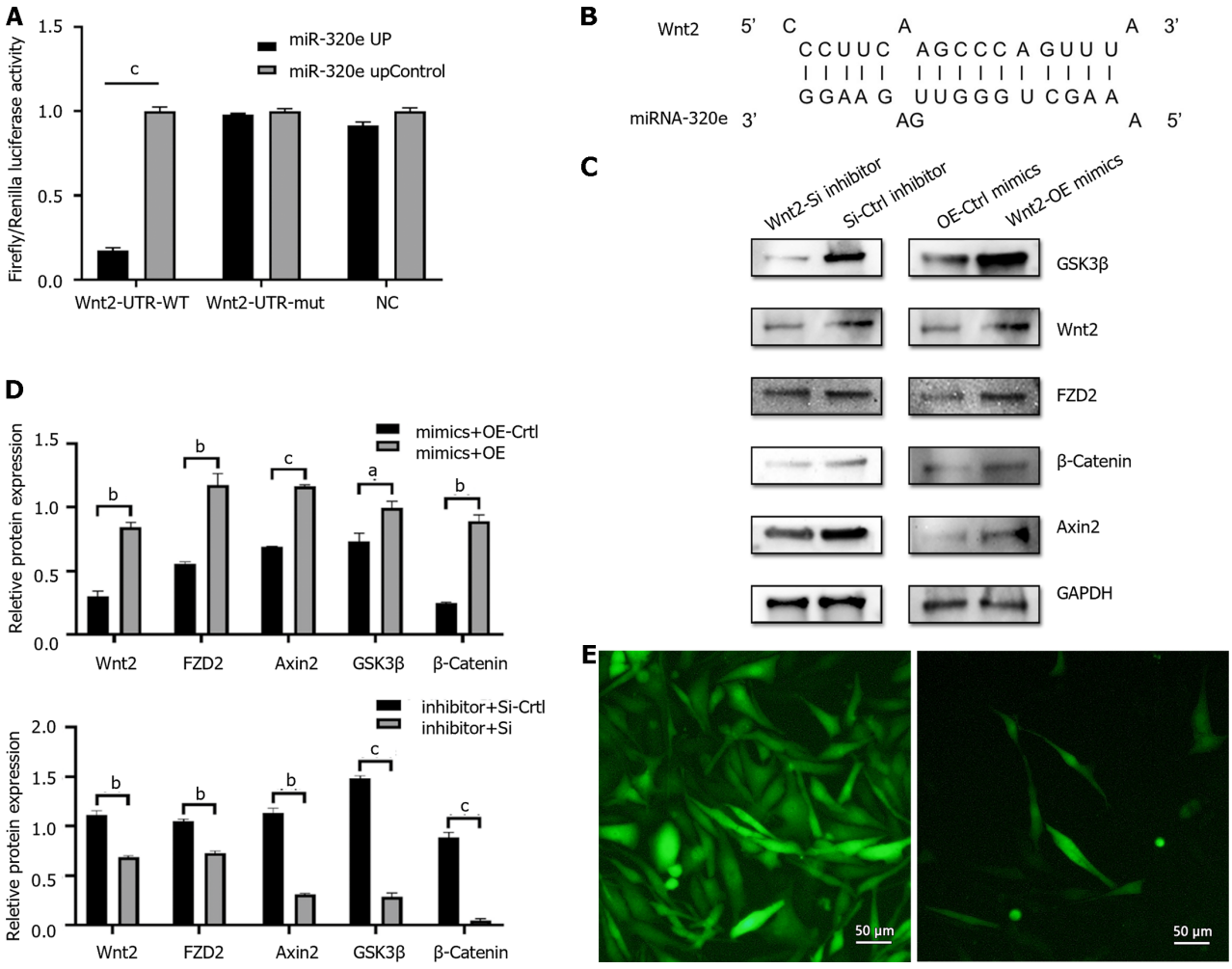
Exosomes could be taken up by endothelial cells and release their loaded miR-320e into the endothelium to bind to Wnt2 for inhibitory effects

HUVECs were cultured using miR-320e mimics (Figure 5A), and the lipid membranes in the system were stained with DiI, a lipophilic stain with red fluorescence. We collected fresh culture medium and extracted the exosomes secreted by HUVECs to treat another group of HUVECs, and then tested the expression of Wnt2 and β-catenin in the exosome-treated and control groups. The results showed that HUVECs could be stained with DiI (Figure 5B), and we detected the collected exosome suspension in a microplate reader. We observed an increase in the absorbance at 550 and 567 nm



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Figure 1 Construction and bioinformatics analysis of differentially expressed miRNA libraries. A: Volcano diagram showing that miRNA-320e was significantly downregulated; B: High-throughput sequencing of plasma exosomes showed that the expression of miR-320e was significantly downregulated; C: Bioinformatics suggested the biological processes involved in differentially expressed miRNAs. Further information was shown in the Supplementary Material.



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Figure 2 miR-320e could bind to Wnt2 to inhibit the Wnt/β-catenin pathway. A: The results of the dual-luciferase reporter gene experiment; B: Binding sequence between Wnt2 mRNA and miR-320e; C and D: Protein blots were listed in the column. After cotransfection of the miR-320e mimic, western blotting showed that Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression increased compared with that of the control group. After cotransfection of the miR-320e inhibitor, western blotting showed that Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression decreased compared with that of the control group; E: Cell image after cotransfection of cells. The image above showed transfection with miR-320e mimic and the one below showed transfection with miR-320e inhibitor. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$.

(Figure 5C). Using the collected exosomes secreted by DiI-stained endothelial cells to treat unstained and treated endothelial cells, we observed red fluorescence in the unstained cells after exosome treatment. In addition, we used these exosomes to treat human aortic vascular smooth muscle cells (HASMCs) and observed red fluorescence in these HASMCs (Figure 5D), indicating that HUVEC-derived exosomes could be secreted into the extracellular environment and taken up by other cells. In the Exo/miR-320e-mimic group, Wnt2 mRNA and β-catenin protein and mRNA levels were lower than those in the control group (Figure 5E-G). The above information proves that exosomes can be taken up by other cells, and miR-320e loaded into exosomes enters the cells and exerts an inhibitory effect on Wnt/β-catenin pathway activation by targeting Wnt2.

Retrospective analysis in patients with CVSD

In the same population for exosome extraction, 80 patients with CVSD (42 men and 38 women) with an average age of 66.3 years were included. The average educational level was 9.2 years. Among these patients, 60 patients had hypertension, 24 patients had diabetes, and 36 patients had hyperlipidemia, while the remaining patients did not have respective diseases. Additionally, 28 patients had a history of smoking and 16 patients had a history of alcohol consumption. At the baseline of disease characteristics, 40 patients (50%) had lacunar infarctions, 20 (25%) had cerebral microbleeds, and 20 (25%) had mixed-type CSVD. The white matter hyperintensity burden of the CVSD patient group at enrollment was 12.5 ± 4.2 cm^3, and the total CSVD burden score was 3.2 ± 1.1 points.

The correlation between exosomal miR-320e levels and psychiatric symptoms in patients with CVSD was characterized by Pearson's correlation analysis, which suggested that miR-320e was positively correlated with both cognitive impairmentrelated MoCA/EFA scores and depression-related HAMD/BDI scores (all $P < 0.05$), as shown in Table 1. Based on the scores for cognitive function and depressive symptoms of patients, we found that patients with relatively severe cognitive impairment and depression had statistically lower expression levels of miR-320e in the extracted exosomes than patients in relatively good condition (all *P*-values < 0.05), as shown in Table 2.

Table 1 Correlation analysis of exosomal miR-320e levels with clinical assessment results in cerebral small vessel disease patients

Variable	Spearman correlation coefficient	*P* value
MoCA score	0.328	0.003
EFA score	0.301	0.006
HAMD score	-0.296	0.007
BDI score	-0.283	0.010

MoCA: Montreal Cognitive Assessment; EFA: Executive Function Assessment; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory.

Table 2 miRNA levels by groups of more and less severe symptoms of cognitive impairment or depress in cerebral small vessel disease patients, *n* (%)

Assessment Scale	More severe disease (below the average score)		Less severe disease (beyond the average score)		*P* value of miRNA-levels
	Patients	miRNA level	Patients	miRNA level	
MoCA	45 (56.25)	1.18 ± 0.32	35 (43.75)	2.15 ± 0.45	0.010
EFA	40 (50)	1.25 ± 0.40	40 (50)	2.30 ± 0.50	0.0092
HAMD	50 (62.5)	1.10 ± 0.35	30 (37.5)	2.20 ± 0.55	0.030
BDI	38 (47.5)	1.15 ± 0.38	42 (52.5)	2.25 ± 0.48	0.0012

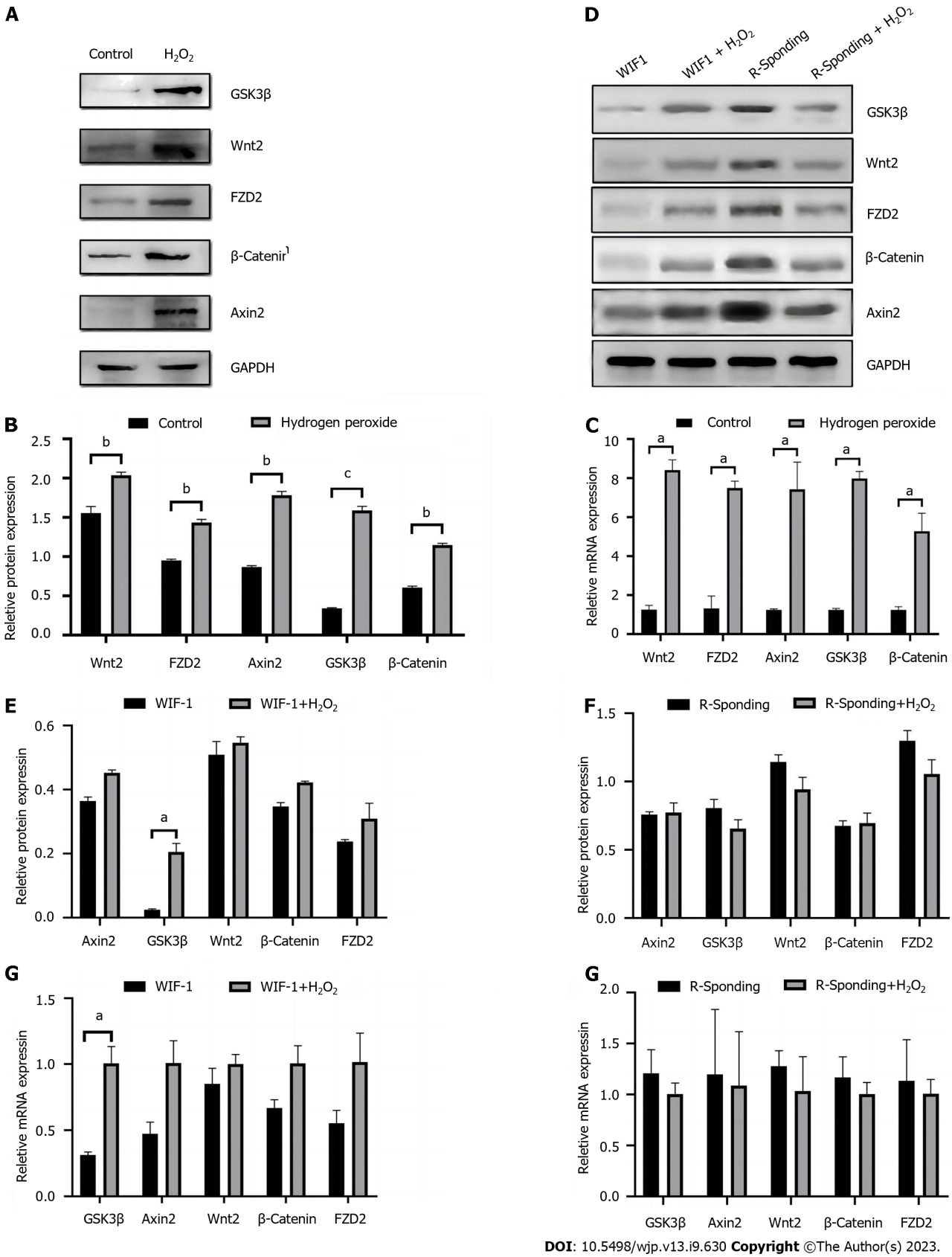
MoCA: Montreal Cognitive Assessment; EFA: Executive Function Assessment; HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory.

DISCUSSION

The Wnt/β-catenin pathway is involved in the response to oxidative stress stimuli and leads to white matter lesions and central nervous system inflammation and injury[26-28]. Inhibition of the abnormal activation of the Wnt/β-catenin pathway was shown to delay coronary artery disease in the myocardial tissue of rats[29] and the process of renal ischaemia-reperfusion injury involving oxidative stress in the kidney[30]. Inhibition of the Wnt/β-catenin pathway also inhibited the progression of neuroblastoma and attenuated axonal degeneration in Parkinson's disease models[20,21,31]. However, studies on the involvement of the Wnt/β-catenin pathway in CVSD are lacking. Based on the widespreadly applied model of HUVECs in the study of cerebral vasculature, our study showed that miR-320e inhibited the oxidative stress-induced Wnt/β-catenin pathway by targeting Wnt2 in endothelial cells to facilitate a protective role in CVSD. The miR320e expression in patients with CVSD was significantly lower in those with relatively severe cognitive impairment and depression, with a positive correlation with both MoCA/EFA and HAMD/BDI scores. Thus, we speculated that miR-320e could be a potential predictive and therapeutic target for CVSD. However, it was important to note that while HUVECs serve as a useful preliminary model, future investigations employing more directly relevant cell types could potentially further reinforce and expand upon our findings.

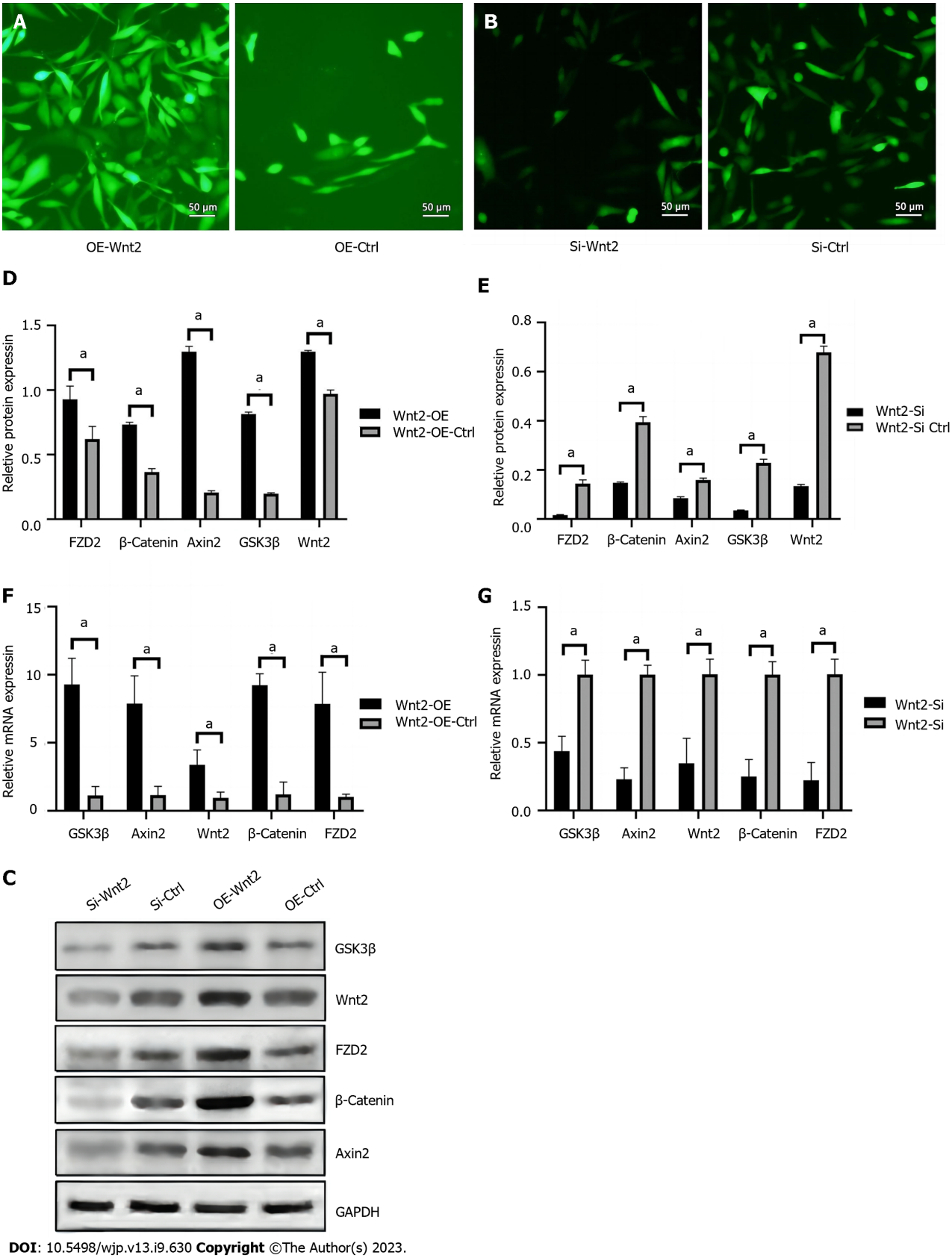
Due to the scarcity or absence of smooth muscle content in small arteries, smallvessel diastolic function and substance screening are dependent on endothelial cells to perform normal physiological functions, which are influenced by a combination of factors[32-35]. Recent studies have shown that exosomes transport complex substances that freely reach and cross the blood-brain barrier (BBB), and the miRNAs carried are protected by the exosome membrane from degradation by RNA enzymes so that they can effectively act on target cells. Thus, exosomal miRNAs are considered to affect cerebrovascular disorders by affecting the microenvironment of intracranial vessels[36,37]. Previous studies have found that neuronal-secreted exosomal miR-132 can regulate cerebrovascular integrity[38], exosomal miR-451a may play a protective role in ischemia-reperfusion injury[13], and exosomal miR-124a from mesenchymal stem cells can target and inhibit FOX A2 to suppress glioblastoma[14]. Our study showed that exosomes could carry miR-320e into HUVECs, allowing miR-320e to target Wnt2 to exert inhibition of the Wnt/β-catenin pathway during oxidative stress.

To verify the inhibitory effect of miR-320e on the Wnt/β-catenin pathway, we detected the binding target of Wnt2 and the downstream components of FZD2, Axin2, GSK3β and total cellular β-catenin. Our experiment showed that the oxidative stressinduced enhanced Wnt/β-catenin pathway was significantly inhibited by miR320e, as evidenced by the significant suppression in the above genes. In addition, exosomes carrying miR-320e exerted a similar inhibitory effect on the Wnt/β-catenin pathway. Furthermore, we found that GSK3β was inhibited by miR-320e to a much lesser extent than the other genes in the Wnt/β-catenin pathway. GSK3β is involved in multiple pathways, in addition to its role in the Wnt/β-catenin pathway, representing a class of components that exert pathway interactions during cell signaling[39], which suggests that other miRNAs carried by the experimental exosomes from patients with CVSD may contribute to disease deterioration through other mechanisms.



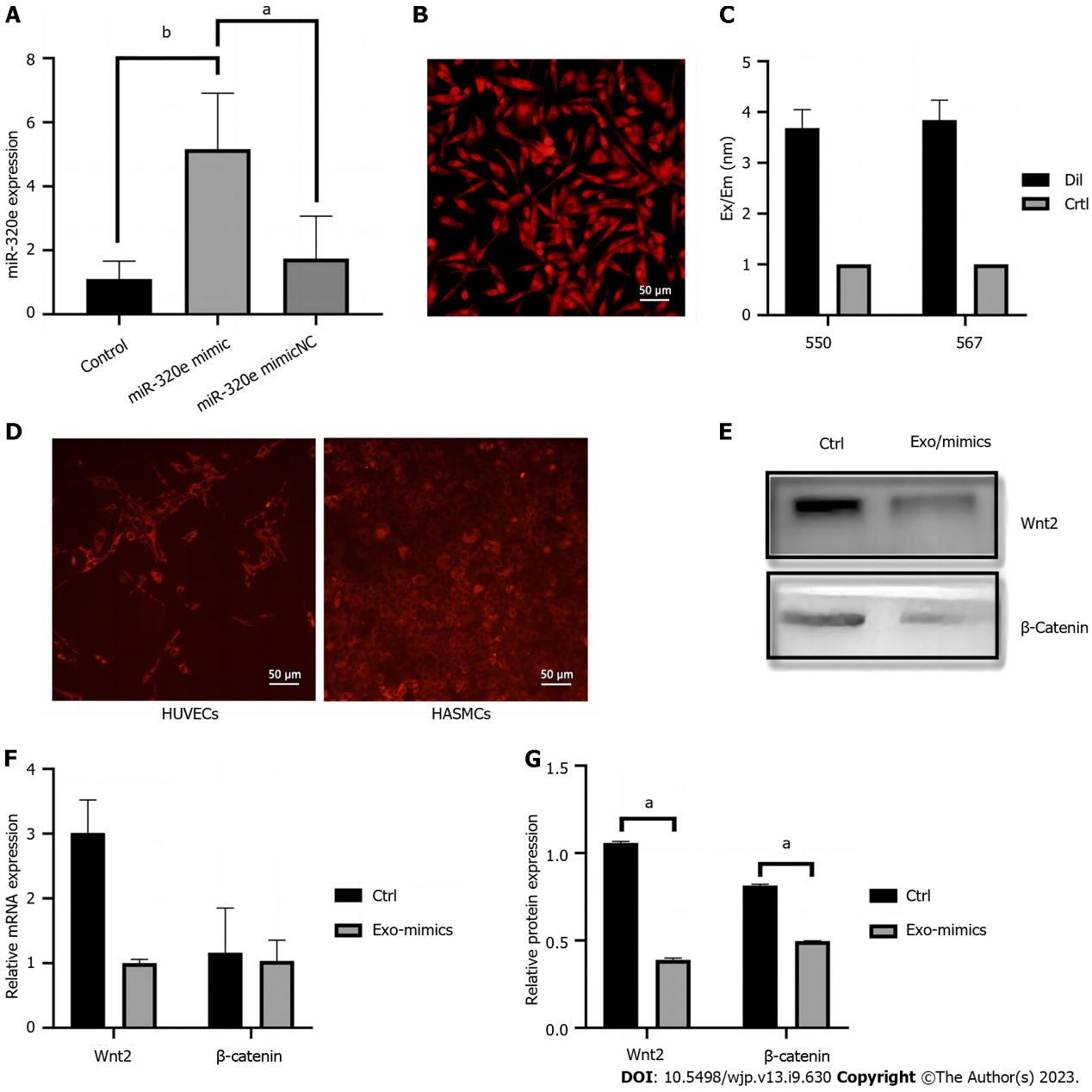
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Figure 3 Representative protein blots of Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression under hydrogen peroxide. A and B: The Western-Blot results showed that Wnt2 expression in the hydrogen peroxide group increased compared to that in the control group; C: The PCR results showed that Wnt2 expression in the hydrogen peroxide group increased compared to that in the control group; D-F: Expression of Wnt2, FZD2, Axin2, GSK3β, and β-catenin expression after treating with WIF1 and R-Spondin under hydrogen peroxide were similar and further enhanced, respectively, compared to that in the groups without hydrogen peroxide; G and H: The PCR results showed that GSK3β in the WIF + H_2O_2 group increased, and the other mRNA expression levels remained similar. PCR: Polymerase chain reaction. $^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$.



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Figure 4 miR-320e inhibited the Wnt/β-catenin pathway through targeting Wnt2. A and B: Cell transfection images were shown; C-E: The Western-Blot results showed that the expression of Wnt2, FZD2, Axin2, GSK3β, and β-catenin in the miR-320e mimics group was inhibited compared to that in the control group, while this inhibition was effectively blocked by Wnt2 silencing compared to the siRNA control; F and G: The results of real-time PCR showed similar trends to the protein levels of Wnt2, FZD2, Axin2, GSK3β, and β-catenin with overexpressed miR-320e and knockdown of Wnt2. PCR: Polymerase chain reaction. $^{a}P < 0.05$.



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Figure 5 The expression of miR-320e in the exosomes secreted by the miR-320e mimic-transfected cells was significantly higher than that in the mimic NC group and the blank control. A: HUVECs were transfected using miR-320e mimics and the expression of miR-320e was detected. B: Lipid membrane of HUVECs marked by DiI; C: Microplate reader analysis showed that exosomes were also marked by DiI; D: As shown by using marked exosomes harvested from HUVECs and cocultured with HASMCs, HUVECs also showed red fluorescence; E-G: Western blotting and PCR showed that Wnt2 and β-catenin expression in the Exo-mimic group decreased compared to that of the control group. HUVECs: Human umbilical vein endothelial cells; HASMCs: Human aortic vascular smooth muscle cells; PCR: Polymerase chain reaction. $^{a}P < 0.05$, $^{b}P < 0.01$.

The Wnt pathway has been suggested to exhibit different responses when subjected to different time frames of oxidative stress, with transiently activated Wnt pathways generally inducing neovascularization and protecting vascular structure and cellular function[40,41], and continuously activated Wnt pathways leading to senescence and basement membrane disruption[42]. In CVSD, when the small vessels that develop lesions are not in critical areas of the white matter or cortex or when CVSD is masked by more severe ischemia and hemorrhage, small vessel lesions can be detected at a more advanced stage, while various aggressive factors may allow sustained activation of Wnt/β-catenin, thus promoting CVSD progression. Because of the ability of exosomal miR-320e to target Wnt2 and thereby inhibit abnormal activation of the Wnt/β-catenin pathway, the significantly lower expression of miR-320e in the plasma exosomes of patients with CVSD may lead to a lack of protection. Moreover, other miRNAs with different expression profiles may exert protective effects when combined with miR-320e, which may guide further investigation and validation.

Normal brain function depends on the integrity of the cerebrovascular system, and several underlying pathophysiological mechanisms have been shown to be involved in CSVD, such as BBB damage, small-vessel stiffness, venous collagen proliferation, inflammation, and myelin damage[43,44]. Endothelial cells are the cornerstone of small vessel function; with the natural onset of aging and the onslaught of various risk factors, intracranial vascular function

gradually declines and structural integrity is gradually lost, which has long been seen as a vital process in CSVD[36,45,46]. Currently, there are only a few studies on the mechanisms of action of exosomal miRNAs in CVSD. In summary, using bioinformatics and clinical retrospective analyses, this study predicted and confirmed that the inhibitory role of Wnt2-targeting miR-320e on the Wnt/β-catenin pathway may protect patients with CVSD from relatively severe cognitive impairment and depression, providing a potential novel predictive and therapeutic target for CVSD.

CONCLUSION

Our study demonstrates that exosomal miR-320e plays a significant role in the pathogenesis of CVSD by regulating the Wnt/β-catenin pathway under oxidative stress. Our findings suggest that exosomal miR-320e may be a potential therapeutic target in CVSD based on its ability to inhibit the Wnt/β-catenin pathway and protect against cognitive impairment and depression. The uptake of exosomes carrying miR-320e can also target Wnt2 and suppress the Wnt2/β-catenin pathway, highlighting the significance of exosomal miRNAs as novel therapeutic agents for CVSD. Further studies are needed to investigate the underlying mechanisms of exosomal miR-320e in CVSD progression and to explore its clinical applications. Overall, this study provides new insights into the complex pathophysiology of CVSD and suggests a promising avenue for developing effective therapies for this devastating disease.

ARTICLE HIGHLIGHTS

Research background

Cerebral small vessel disease (CVSD) is a common neurodegenerative disorder characterized by cognitive impairment and depression. Exosomal miRNAs play an essential role in the pathophysiology of CVSD, and their dysregulation contributes to disease progression. This study aimed to investigate the potential role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and its clinical correlation with cognitive impairment and depression in patients with CVSD. The study utilized high-throughput sequencing, bioinformatics analysis, dual-luciferase reporter gene experiments, and retrospective analysis among patients with CVSD. The aim was to explore whether exosomal miR-320e could suppress the Wnt/β-catenin pathway and play a protective role in CVSD progression, as well as examine its potential correlation with cognitive impairment and depression in patients with CVSD. The findings suggest that exosomal miR-320e targets Wnt2 and inhibits the Wnt/β-catenin pathway in response to oxidative stress, potentially playing a protective role in CVSD progression. Elevated miR-320e expression may also correlate with less severe cognitive impairment and depression in patients with CVSD.

Research motivation

CVSD is a complex neurodegenerative disorder that affects cognitive function and mental health, but currently lacks effective treatments. Exosomal miRNAs are emerging as important regulators of physiological and pathological processes in the brain, including CVSD. This study aimed to investigate the potential role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and its clinical correlation with cognitive impairment and depression in patients with CVSD. The study utilized high-throughput sequencing, bioinformatics analysis, dual-luciferase reporter gene experiments, and retrospective analysis among patients with CVSD. The aim was to explore whether exosomal miR-320e could suppress the Wnt/β-catenin pathway and play a protective role in CVSD progression, as well as examine its potential correlation with cognitive impairment and depression in patients with CVSD. The findings suggest that exosomal miR-320e has a potentially protective role in CVSD progression and may be a novel therapeutic target. The study provides further insights into the complex pathophysiology of CVSD and highlights the importance of exosomal miRNAs in neurological diseases.

Research objectives

The research objectives of this study were to explore the potential role of exosomal miR-320e in the Wnt/β-catenin pathway stimulated by oxidative stress and its clinical correlation with cognitive impairment and depression in patients with cerebral small vessel disease (CVSD). The study aimed to identify differentially expressed exosomal miRNAs by sequencing plasma exosomes from patients with CVSD and healthy controls, confirm the binding of miR-320e to Wnt2 through bioinformatics and dual luciferase analyses, evaluate the mRNA and protein levels of downstream components in the Wnt/β-catenin pathway when overexpressed or knocked down miR-320e under H_2O_2-induced oxidative stress, and conduct a retrospective analysis among patients with CVSD to confirm the relationship between miR-320e expression and the severity of cognitive impairment and depression. The study also aimed to investigate whether exosomal miR-320e could inhibit the Wnt/β-catenin pathway and play a protective role in CVSD progression, potentially leading to the development of novel therapeutic targets for this complex neurodegenerative disorder.

Research methods

The study utilized various methods to investigate the role of exosomal miR-320e in CVSD. Differentially expressed exosomal miRNAs were identified by sequencing plasma exosomes from patients with CVSD and healthy controls. Bioinformatics analysis and dual-luciferase reporter gene experiments were conducted to confirm the binding of miR-

320e to Wnt2. The mRNA and protein levels of downstream components in the Wnt/β-catenin pathway were evaluated through overexpression or knockdown of miR-320e under H_2O_2-induced oxidative stress. Wnt2-targeting siRNA was used to confirm the role of miR-320e in the Wnt2-mediated inhibition of the Wnt/β-catenin pathway. A retrospective analysis was conducted among patients with CVSD to assess the correlation between miR-320e expression and cognitive impairment and depression, which were quantified using the Montreal Cognitive Assessment (MoCA)/Executive Function Assessment (EFA) and the Hamilton Depression Scale (HAMD)/Beck Depression Inventory (BDI), respectively. Overall, these methods provided valuable insights into the potential role of exosomal miR-320e in the pathophysiology of CVSD and its potential clinical significance.

Research results

The results of the study indicate that exosomal miR-320e is downregulated in patients with CVSD. Exosomal miR-320e was found to inhibit the Wnt/β-catenin pathway in response to oxidative stress by targeting the 3' noncoding region of Wnt2. Uptake of exosomes carrying miR-320e could also target Wnt2 and inhibit the Wnt2/β-catenin pathway in endothelial cells. The study also found that elevated miR-320e expression may protect patients with CVSD from relatively severe cognitive impairment and depression, as it had a positive correlation with the MoCA/EFA and HAMD/BDI scores. These findings suggest that exosomal miR-320e may have a potentially protective role in CVSD progression and could be a novel therapeutic target for this complex neurodegenerative disorder. Overall, the results provide important insights into the pathophysiology of CVSD and highlight the importance of exosomal miRNAs in neurological diseases.

Research conclusions

The study found that exosomal miR-320e is downregulated in patients with CVSD and may play a crucial role in the progression of the disease. Exosomal miR-320e was found to inhibit the Wnt/β-catenin pathway by targeting the 3' noncoding region of Wnt2 in response to oxidative stress. The uptake of exosomes carrying miR-320e could also target Wnt2 and inhibit the Wnt2/β-catenin pathway in endothelial cells. Furthermore, elevated miR-320e expression was found to have a positive correlation with cognitive function and depression scores, suggesting it may protect patients from severe cognitive impairment and depression. The study provides new insights into the pathophysiology of CVSD and highlights the potential clinical significance of exosomal miRNAs in neurological diseases. These findings have implications for the development of novel therapeutic targets for CVSD and may provide hope for patients with this complex neurodegenerative disorder.

Research perspectives

The study provides valuable insights into the potential role of exosomal miR-320e in the pathophysiology of CVSD. Future research could investigate the use of exosomal miR-320e as a therapeutic target to prevent or delay the progression of CVSD. Further studies could also investigate the underlying mechanisms by which miR-320e regulates the Wnt/β-catenin pathway and how it affects cognitive function and depression. In addition, the use of animal models could provide further insight into the potential clinical significance of exosomal miRNAs in neurological diseases. Further research could also explore the potential diagnostic and prognostic value of miR-320e in patients with CVSD. Overall, the findings of this study pave the way for future research on the role of exosomal miRNAs in CVSD and other neurodegenerative disorders.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Application of traditional Chinese medicine acupoint needle embedding combined with emotional nursing in patients with gynecological malignant tumors

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Abstract

BACKGROUND

Few relevant literature reports on applying acupoint press-needle embedding combined with emotional nursing in patients with a gynecological malignant tumor.

AIM

To explore the effect of traditional Chinese medicine acupoint needle embedding combined with emotional nursing on chemotherapy-related nausea and vomiting (CINV), cancer-related fatigue (CRF) and psychological state in patients with gynecological malignant tumors.

METHODS

Retrospective analysis of the clinical information of 84 patients with gynecological malignant tumors treated in our hospital from August 2020 to December 2022 Led to the development of an observation group (n = 42) and a control group (n = 42) based on various nursing approaches. Ondansetron hydrochloride injection was administered to the individuals in the control group. However, the observation group received emotional nursing based on the control group and acupoint press-needle embedding of traditional Chinese medicine. Patients in both groups received the chemotherapy regimen of paclitaxel liposome + carbo-platin/cisplatin. For four weeks, both groups intervened. The CINV grade, quality of life, CRF, psychological status and sleep quality scores of the two groups before and

after intervention were compared.

RESULTS

After intervention, the degree of CINV in the observation group was significantly better than that in the control group. After intervention, the scores of each dimension and total score of FLIE scale were significantly higher than those in the control group. After intervention, the scores of each dimension and total score of Piper Fatigue Scale were significantly lower than those in the control group ($P < 0.05$). After intervention, the scores of avoidance and yield dimensions in the observation group were significantly lower than those in the control group, and the scores of confrontation dimension were significantly higher than those in the control group ($P < 0.05$). After intervention, the sleep quality score of the observation group was significantly lower than that of the control group, and the Karnofsky Performance Status scale score was significantly higher than that of the control group ($P < 0.05$).

CONCLUSION

The acupuncture point needle embedding of traditional Chinese medicine combined with emotional nursing can further reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, adopt a positive way to face the disease and treatment, and improve the quality of sleep and quality of life.

Key Words: Press-needle; Acupoint; Emotional nursing; Gynecologic malignant tumor; Sleep quality; Chemotherapy-induced nausea and vomiting; Cancer-related fatigue; Mental state

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Core Tip: Nausea, vomiting and cancer-related fatigue (CRF) are the most common symptoms during chemotherapy in patients with gynecological malignant tumors. If timely and effective nursing intervention is not given, it is easy to affect the quality of life of patients. Acupressure needle has the advantages of simple operation, safety and convenience, while emotional nursing can effectively alleviate the negative emotions of patients with malignant tumors during chemotherapy. The combination of the two can effectively reduce the incidence of nausea and vomiting, improve the quality of life and the degree of CRF in patients with gynecological malignant tumors.

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INTRODUCTION

Cervical, ovarian, and endometrial cancer are the three most prevalent gynecological malignancies, accounting for approximately 18% of all tumors worldwide[1]. The incidence rate has been rising recently, significantly negatively affecting women's physical and emotional health. Chemotherapy, which can efficiently eliminate cancerous cells and increase patients' overall survival times, is currently the preferred clinical treatment technique. However, while treating diseases, chemotherapy can also suppress normal cells, resulting in the suppression of the immune function of patients and negative responses, such as vomiting and nausea, peripheral neurotoxicity, a decrease in hematopoietic stem cell level, *etc*[2], as well as cancer-related fatigue (CRF), thus affecting patients' chemotherapy compliance. Chemotherapy-induced nausea and vomiting (CINV), which can occur in up to 70% of patients with gynecological malignant tumors during chemotherapy, is the most common adverse response. If not prevented and treated promptly and effectively, it can easily lead to eating difficulties in patients and even an imbalance of water, electrolyte, and acid-base balance in severe cases[3]. CRF is a term used to describe severe, continuous, psychological fatigue in physical, emotional, or cognitive aspects unrelated to recent activities caused by a tumor or tumor treatment and interferes with everyday activities. According to incomplete statistics[4], about 57.84% of patients with gynecological malignant tumors will have CRF during chemotherapy, which is easy to increase the pain of patients and affect the quality of sleep and life. Western medicine mainly uses 5-HT3 receptor antagonists, NK-1 receptor blockers, glucocorticoids and other drugs to treat CINV, which can effectively prevent patients from developing CINV. Still, some patients are prone to constipation, headache and other adverse reactions after Western medicine treatment[5].

Traditional Chinese medicine (TCM) has an extensive history of treating gastrointestinal side effects brought on by chemotherapy and offers the benefits of safe use, ease of use, cheap cost, and lack of side effects, *etc.* The external treatment of traditional Chinese medicine has formed a systematic theory and specific methods in developing traditional Chinese medicine for thousands of years, mainly including press-needle embedding, acupoint application, acupuncture, emotional therapy, *etc.* Acupoint press-needle embedding is a type of external treatment of TCM, which can induce continuous weak stimulation at the acupoint by penetrating the needle into the subcutaneous area of a specific acupoint

[6]. It has the advantages of simple operation, safety and convenience. Emotional nursing is a type of TCM nursing technology that consists of the language guidance method, emotion inter-resistance treatment, and emotional desire adjustment. It can easily relieve the negative emotions of cancer patients undergoing chemotherapy[7]. Few relevant literature reports on applying acupoint press-needle embedding combined with emotional nursing in patients with a gynecological malignant tumor. The clinical effectiveness of acupoint press-needle embedding and emotional nursing in individuals with gynecological cancer is examined in this study using a retrospective analysis method.

MATERIALS AND METHODS

Clinical data

A retrospective analysis was done on the clinical data of 84 patients who received chemotherapy for gynecological malignant tumors at our institution between August 2020 and December 2022. (1) Inclusion criteria: Aged 18-80 years old; the patient was diagnosed with a gynecological malignant tumor by postoperative pathological and cytological examination. Patients who needed chemotherapy; Karnofsky Performance Status scale (KPS) score ≥ 70 points; No other antiemetic drugs were taken 48 h before chemotherapy; Complete clinical data; and (2) Exclusion criteria: Patients with liver and kidney insufficiency; Nausea and vomiting caused by intracranial hypertension, vestibular dysfunction and digestive system diseases; Those with contraindications to press-needle; Mental disorders and cognitive disorders; incomplete case data. The 84 patients were grouped into a control group (n = 42) and an observation group (n = 42) using various nursing techniques.

Methods

Liposome + carboplatin/cisplatin. The control group was given an injection of 0.9% sodium chloride (Sichuan Kelun Pharmaceutical Co., Ltd., Approval No. H20056626), a 100 mL injection of ondansetron hydrochloride [Qilu Pharmaceutical Co., Ltd., (No. H10970065)], and 8 mg intravenously 15 min before chemotherapy. Based on the control group, the observation group received acupoint press-needle embedding treatment and emotional nursing. The acupoints of Guanyuan, Dazhui, bilateral Geshu, Zusanli and Shenshu were selected for press-needle treatment, used alcohol to disinfect the patient's skin at the corresponding acupoint, used tweezers to remove the disposable press-needle, quickly attached the press-needle to the acupoint, pressed and smoothed. The operation was performed at the beginning of chemotherapy, the patient was instructed to press intermittently during treatment, the needle could be removed after 2 d, and the press-needle embedding therapy was performed once every 3 d. Emotional nursing: Chinese medical nursing staff carried out emotional nursing, kept the indoor environment in a calm and bright state, and adopted emotional nursing methods such as language guidance method, emotion inter-resistance therapy, emotional transference method, calming mind method, and emotional desire adjustment: (1) Language guidance method: Following the start of chemotherapy, the responsible nurse assessed the patient's mental health and identified the root reasons for their depression, 30 min for each time; (2) Emotion inter-resistance therapy: After chemotherapy, music therapy was used to help patients relieve negative emotions, guided patients to watch skits, cross talk and other programs, and helped patients increase joy to reduce the sadness of patients; and (3) Emotional transference method: Guided patients to find their interests and hobbies, and transfer their attention to chemotherapy through painting, calligraphy, walking and other ways to alleviate bad emotions. The responsible nurse selected 2-3 emotional nursing methods daily and operated once daily. Both groups were treated for 4 wk.

Observation indicators

Between the two groups, comparisons were made of the basic information, CINV grade, quality of life, CRF, coping style, and sleep quality scores: (1) General data questionnaire: including age, education level, primary tumor site, initial chemotherapy, KPS score and other clinical data; (2) CINV grade classification: Grade 0: No nausea or vomiting; Grade I: Nausea but no vomiting; Grade II: Intermittent vomiting with nausea; Grade III: Vomiting Needs Treatment; Grade IV: Excessive vomiting; CINV grades were assigned on the basis of patient's nausea and vomiting[8]; (3) Quality of life (QoL): The QoL of both groups before and after the intervention was evaluated by the Functional Living Index-Emesis (FLIE)[9], which was divided into two dimensions: nausea and vomiting. Each dimension had 9 items, each scoring according to 1 to 7 levels. The higher the score, the smaller the impact of CINV on functional living; (4) CRF: The Chinese version of the Revised Piper Fatigue Scale (PFS-R)[10] was employed to examine the level of fatigue in the two groups before and following the intervention. It consists of 22 questions and is categorized as follows: Behavior, emotion, perception, and cognition; (5) Mental state: The medical coping style scale[11] was applied to determine the coping style of both groups before and after the intervention, which was divided into three dimensions: Avoidance, yield and facing, with 20 items. The higher the score of each dimension, the more likely the patient was to adopt the coping style; and (6) Sleep quality: The Pittsburgh Sleep Quality Index (PSQI)[12] was utilized to examine 18 items, including seven aspects of sleep latency, sleep duration, sleep efficiency, sleep disorders, hypnotic drugs, and daily dysfunction. The scale ranged from 0 to 21, and the overall score was the average for each item. A total score of ≤ 7 suggested normal sleep quality and sleep disorders by a total score of ≥ 8. The lower the patient's sleep quality, the higher the overall score.

Data collection

Nursing staff who had been trained in a unified manner distributed the general information questionnaire and scales of quality of life, CRF, coping style, and sleep quality to the patients, explained the purpose of this study and the

precautions for filling in the patients before filling in, and checked whether the questionnaire and scale were missing after filling in to ensure the integrity of the questionnaire and scale.

Statistical analysis

In this study, EpiData 3.0 software was used to input data by two people. The data obtained were analyzed and processed with SPSS25.0 software. The counting data is presented as "n (%)", and the comparison was made using the chi-square test. The measurement data following the normal distribution were presented as mean ± SD, and the t-test was employed for comparison. A P value < 0.05 was deemed as statistically significant for all analyses.

RESULTS

General data comparison between the two groups

Table 1 demonstrates no statistically considerable variation in the basic data of both groups (P > 0.05).

The CINV score comparison in both groups following treatment

Following the intervention, the observation group's CINV grade was considerably higher as compared to the control group (P < 0.05; Table 2).

Comparison of pre-and post-intervention QoL values in both groups

The scores for each dimension and the FLIE scale's overall score before intervention did not significantly vary (P > 0.05) in both groups. With statistical significance (P < 0.05), the scores for each component and the overall FLIE scale score in the two groups were higher after the intervention. Following the intervention, the observation group's scores on each component and overall FLIE scale score were significantly higher than those of the control group (P < 0.05; Table 3).

Comparison of CRF scores before and after intervention for both groups

Before the intervention, there was no statistically significant difference (P > 0.05) between the scores of each dimension and the total score on the PFS-R scale in both groups. After the intervention, the scores of each dimension and the total score of the PFS-R scale in the observation group were considerably lower than before the intervention (P < 0.05). In contrast, the scores of each dimension and the total score of the PFS-R scale of the control group pre- and post-the intervention did not demonstrate statistical significance (P > 0.05). Table 4 shows that after the intervention, the score of each dimension and the overall score of the PFS-R scale in the observation group were significantly lower compared to the control group (P < 0.05).

Comparison of coping style ratings before and after intervention in both groups

Before the intervention, no significant difference (P > 0.05) in the scores of medical coping strategies in both groups was observed. Both groups' avoidance and yield dimensions dropped after the intervention compared to before. The scores on the facing dimension improved (P < 0.05) compared to those before the intervention. Following the intervention, the observation group's scores for the avoidance and yield dimensions were significantly lower than those of the control group. The face dimension score was significantly higher compared to the control group (P < 0.05; Table 5).

Evaluation of both groups' KPS scores and sleep quality pre- and post-intervention

Both groups had no significant change (P > 0.05) before the intervention in sleep quality or KPS score. Both groups' sleep quality and KPS scores dropped significantly (P < 0.05) after the intervention compared to before. As shown in Table 6, the observation group's sleep quality score was considerably lower than the control group's after the intervention, while the control group's KPS score was significantly higher (P < 0.05).

DISCUSSION

Epidemiological research shows that[13] the number of patients diagnosed with gynecological malignancies and the number of deaths from such diseases are increasing yearly and have obvious characteristics such as low age and high malignancy, which seriously affect the physical and social psychological health of contemporary women. There are many treatments for gynecological malignant tumors. Adjuvant chemotherapy is an important measure to improve the postoperative survival rate. Since vomiting and nausea are frequent side effects of chemotherapy, therapeutic attention has turned to preventing and treating CINV. Previous clinical studies have suggested that the vomiting mechanism is complex, mainly because the neurotransmitter receptors on the gastrointestinal pheochromocytoma combine with chemotherapy drugs to stimulate the brain centre and send signals to the organs and tissues of the upper digestive tract to complete the vomiting reflex. Among them, important neurotransmitters such as 5-HT and substance P participate in the reaction and bind to the 5-HT_3 receptor and NK-1 receptor, respectively[14].

Therefore, Western medicine often uses 5-HT3 receptor antagonists and NK-1 receptor blockers to prevent nausea and vomiting[15], but long-term use is prone to adverse reactions. Compared with traditional acupuncture, the diameter of the press needle is generally about 0.20 mm, and the length of the needle body varies from 0.30 to 5.00 mm. After the

Table 1 shows the comparisons of demographic data between the two groups, *n* (%)

Item		Observation group (*n* = 42)	Control group (*n* = 42)	t/χ^2 value	*P* value
Age (yr, mean ± SD)		52.49 ± 7.65	52.18 ± 7.83	0.184	0.855
Primary tumor site	Ovarian cancer	14 (33.33)	15 (35.71)	0.236	0.889
	Endometrial carcinoma	3 (7.14)	2 (4.76)		
	Cervical cancer	25 (59.52)	25 (59.52)		
Primary chemotherapy	Yes	18 (42.86)	17 (40.48)	0.049	0.221
	No	24 (57.14)	25 (59.52)		
KPS score (points, mean ± SD)		82.56 ± 5.69	82.33 ± 5.87	0.182	0.856

KPS: Karnofsky Performance Status scale.

Table 2 Comparison of chemotherapy-related nausea and vomiting grade between the two groups after intervention, *n* (%)

Group	*n*	Grade 0	Grade I	Grade II	Grade III	Grade IV
Observation group	42	29 (69.05)	10 (23.81)	2 (4.76)	1 (2.38)	0 (0.00)
Control group	42	15 (35.71)	13 (30.95)	8 (19.05)	5 (11.90)	1 (2.38)
χ^2 value		12.114				
P value		0.017				

Table 3 Compares both group's quality of life scores before and after the intervention

Group	*n*	Nausea dimension		Vomiting dimension		Total score	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group	42	32.30 ± 6.54	40.23 ± 4.52[a]	32.77 ± 6.81	39.87 ± 5.36[a]	63.54 ± 7.81	80.15 ± 6.52[a]
Control group	42	32.08 ± 3.77	33.89 ± 3.59[a]	32.59 ± 6.94	33.72 ± 5.47[a]	63.37 ± 7.95	74.58 ± 7.16[a]
t value		0.189	7.118	0.120	5.204	0.099	3.728
P value		0.851	0.000	0.905	0.000	0.921	0.000

[a]$P < 0.05$.

Table 4 Comparison of cancer-related fatigue scores between both groups before and after intervention (points mean ± SD)

Group	*n*	Behavior		Emotion		Perception		Cognition		Total score	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	After intervention
Observation group	42	3.84 ± 0.57	3.12 ± 0.84[1]	3.91 ± 0.62	2.74 ± 0.36[1]	3.74 ± 0.55	2.78 ± 0.67[1]	3.91 ± 0.32	2.68 ± 0.36[1]	4.11 ± 0.36	2.33 ± 0.41[1]
Control group	42	3.67 ± 0.69	4.64 ± 0.97	3.85 ± 0.72	3.94 ± 0.47	3.66 ± 0.63	3.82 ± 0.54	3.88 ± 0.49	3.97 ± 0.52	3.94 ± 0.48	3.99 ± 0.56
t value		1.231	7.677	0.409	13.136	0.62	7.832	0.332	13.219	1.836	15.5
P value		0.222	0	0.683	0	0.536	0	0.741	0	0.07	0

[1]Indicates significant value.

Table 5 Comparison of coping style scores between the two groups before and after intervention (points mean ± SD)

Group	*n*	Avoidance		Yield		Facing	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group	42	18.56 ± 1.25	11.21 ± 1.08[a]	17.54 ± 1.37	10.23 ± 1.55[a]	11.27 ± 1.58	19.52 ± 1.13[a]
Control group	42	18.41 ± 1.38	13.64 ± 2.55[a]	17.28 ± 1.49	12.19 ± 1.12[a]	11.09 ± 1.67	14.16 ± 1.29[a]
t value		0.522	5.687	0.832	6.642	0.507	20.255
P value		0.603	0.000	0.408	0.000	0.613	0.000

[a]$P < 0.05$.

Table 6 Comparison of sleep quality and Karnofsky Performance Status scale score between the two groups before and after intervention (points mean ± SD)

Group	*n*	PSQI scale		KPS score	
		Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group	42	12.24 ± 2.57	6.54 ± 1.57[a]	82.56 ± 5.69	79.85 ± 6.62[a]
Control group	42	11.97 ± 2.98	9.51 ± 1.68[a]	82.33 ± 5.87	75.71 ± 7.52[a]
t value		0.445	8.371	0.182	2.678
P value		0.658	0.000	0.856	0.009

[a]$P < 0.05$.
PSQI: Pittsburgh Sleep Quality Index; KPS: Karnofsky Performance Status.

needle is inserted into the human body, there is almost no sense of acupuncture. After the needle is applied, it is buried in the body with glue and can be retained for a long time. It has the advantages of simple operation and low price. Traditional Chinese medicine acupoint press needles can achieve a sustained therapeutic effect by continuously stimulating the body and then prolonging the effect of acupuncture[15]. Previous studies have found that[16] applying an acupoint press needle in patients with dermatitis helps promote the blood circulation of patients and has a good analgesic effect. Emotional nursing affects patients' emotions through the words and behaviors of medical staff, thus improving patients' negative emotions, eliminating patients' worries and anxieties, and improving patients' anti-cancer concepts.

This study applied acupoint press needle and emotional nursing to gynecological malignant tumor patients receiving chemotherapy. The results showed that the observation group's post-intervention FLIE scale scores on each dimension and overall were considerably higher compared to the control group and that the observation group's post-intervention CINV grade was higher than that of the control group. The findings indicated that emotional nursing and acupoint press-needle embedding could further lower the prevalence of CINV in patients with gynecological malignant tumors and lessen the negative effects of nausea and vomiting on quality of life. CRF is a subjective feeling often associated with cancer patients. Unlike other common symptoms, CRF does not have obvious physiological changes or measurable physiological indicators[17].

Meanwhile, Chinese women are more tolerant and often hide their fatigue performance to avoid burdening their families, mistakenly believing that fatigue is only temporary. However, studies have shown[18] that persistent CRF leads to a higher risk of death. The findings of this research demonstrated that after the intervention, the observation group's PFS-R scale scores on each dimension and overall were lower than the control group. The statistical significance of the difference suggests that acupoint press-needle embedding combined with emotional caregiving can help reduce the severity of CRF in patients with gynecological cancerous tumors. The study's findings also revealed that the observation group's avoidance and yield dimension scores were significantly lower after the intervention than those of the control group.

Compared to the control group, their face dimension scores were significantly higher, their sleep quality scores were significantly lower, and their KPS scores were higher, indicating that the acupoint press-needle embedding combined therapy had an effect. The acupoint press-needle embedding may produce constant stimulation on particular acupoints, which can have the effect of antiemesis and lessen the negative effects of CINV on quality of life. With emotional nursing measures, the language guidance method, emotion inter-resistance therapy, emotional transference method, calming mind method and other methods were used to relieve the bad mood of patients. Music therapy was used to improve the cerebral cortex excitability to regulate the human body's mood, thus eliminating the tension, anxiety and other feelings of the human body, improving fatigue degree and sleep quality, and establishing confidence in treating disease.

CONCLUSION

In conclusion, Chinese medicine acupoint needle embedding combined with emotional nursing can further reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, and adopt a positive way to face the disease and treatment, improve sleep quality and quality of life, which is worthy of clinical application.

ARTICLE HIGHLIGHTS

Research background

The number of patients diagnosed with gynecological malignant tumors and the number of deaths from such diseases are increasing year by year. At the same time, it has obvious characteristics such as low age and high malignancy, which seriously affects the physical and social mental health of contemporary women. Nausea and vomiting are common adverse reactions after chemotherapy. Therefore, preventing and improving chemotherapy-related nausea and vomiting has become a hot topic in clinical research. In the past, 5-HT3 receptor antagonists, NK-1 receptor blockers and other drugs were used to prevent nausea and vomiting, but long-term use was prone to adverse reactions. The use of traditional Chinese medicine nursing measures has the advantages of simple operation and good safety.

Research motivation

To observe the application value of traditional Chinese medicine acupoint needle embedding combined with emotional nursing in improving the adverse reactions of gynecological malignant tumor chemotherapy, which can effectively reduce the incidence of nausea and vomiting and cancer-related fatigue (CRF) caused by chemotherapy, improve the treatment confidence and improve the prognosis of patients.

Research objectives

By observing the effect of traditional Chinese medicine acupoint needle embedding combined with emotional nursing on chemotherapy-related nausea and vomiting, CRF and psychological state in patients with gynecological malignant tumors, it is helpful to reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, adopt a positive and positive way to face the disease and treatment, and improve the quality of sleep and quality of life.

Research methods

By observing the effect of traditional Chinese medicine acupoint needle embedding combined with emotional nursing on chemotherapy-related nausea and vomiting, CRF and psychological state in patients with gynecological malignant tumors, it is helpful to reduce the incidence of chemotherapy-related nausea and vomiting in patients with gynecological malignant tumors, improve the quality of life and the degree of CRF, alleviate the bad psychological state, adopt a positive and positive way to face the disease and treatment, and improve the quality of sleep and quality of life.

Research results

By observing the application value of traditional Chinese medicine acupoint needle embedding combined with emotional nursing in patients with gynecological malignant tumors, it was found that acupoint needle embedding combined with emotional nursing had significant effects on reducing the incidence of adverse reactions to chemotherapy, improving CRF and quality of life of patients. The effect of this program on the long-term prognosis of patients with gynecological tumors still needs to be further verified.

Research conclusions

Traditional Chinese medicine nursing program is of great significance to reduce the incidence of adverse reactions of chemotherapy in patients with gynecological malignant tumors and improve their quality of life.

Research perspectives

In the future, it is necessary to further observe the effect of traditional Chinese medicine nursing technology on improving the long-term prognosis of patients with gynecological malignant tumors.

FOOTNOTES

Author contributions: Ren Z initiated the project and designed the experiment; Cui W conducted clinical data collection; Li YP performed postoperative follow-up and recorded data; Ren Z conducted a number of collation and statistical analysis; Cui W wrote the original manuscript; Li YP revised the paper; all authors reviewed and approved the paper, and read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of factors related to postpartum depression in pregnancy-induced hypertension syndrome patients and construction and evaluation of nomograms

Jie-Wei Pan, Gang Zhao

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Abstract

BACKGROUND

It is positive to integrate and evaluate the risk factors for postpartum depression in patients with pregnancy-induced hypertension syndrome and to detect high-risk patients as early as possible, which has application value for the clinical development of personalized prevention programs and prognosis of patients.

AIM

To analyze factors related to postpartum depression in patients with pregnancy-induced hypertension and construct and evaluate a nomogram model.

METHODS

The clinical data of 276 patients with pregnancy-induced hypertension admitted to Huzhou Maternity and Child Health Care Hospital between January 2017 and April 2022 were retrospectively analyzed. We evaluated the depression incidence at 6 wk postpartum. The depression group included patients with postpartum depression, and the remainder were in the non-depression group. Multivariate logistic regression analysis and the LASSO regression model were applied to analyze the factors related to postpartum depression in patients with pregnancy-induced hypertension. After that, a risk prediction model nomogram was constructed and evaluated.

RESULTS

Multivariate logistic regression analysis showed that vitamin A deficiency (VAD) during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were independent risk factors for postpartum depression in patients with pregnancy-induced hypertension ($P < 0.05$). We constructed the nomogram model based on these five risk factors. The area under the curve, specificity, and

sensitivity of the model in predicting postpartum depression in patients with pregnancy-induced hypertension was 0.867 (95% confidence interval: 0.828–0.935), 0.676, and 0.889, respectively. The average absolute error was 0.037 (Hosmer-Lemeshow test χ^2 = 10.739, P = 0.217).

CONCLUSION
VAD during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, EPA, and DHA affect postpartum depression in patients with pregnancy-induced hypertension.

Key Words: Pregnancy-induced hypertension syndrome; Postpartum depression; Unhealthy emotions; Related factors; Nomograms; Evaluation

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Core Tip: Pregnancy-induced hypertension usually manifests as an elevation of blood pressure, oedema, multiple organ damage, eclampsia, and even coma. Here, we analyzed the factors related to postpartum depression in patients with pregnancy-induced hypertension. We used vitamin A deficiency during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, eicosapentaenoic acid, and docosahexaenoic acid to construct a nomogram evaluated and confirmed to have good predictive performance. It is a breakthrough in the prediction of postpartum depression in pregnancy-induced hypertension.

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INTRODUCTION

Pregnancy-induced hypertension is a syndrome caused by elevated blood pressure, with a prevalence of 12%[1]. Elevation of blood pressure, oedema, multiple organ damage, eclampsia, and even coma are common clinical symptoms in patients with pregnancy-induced hypertension, which can increase the risk of maternal and perinatal death. Postpartum depression includes negative emotions such as pessimism, anxiety, loss, and ease of fright after childbirth. In severe cases, there may be suicidal tendencies and dangerous events such as harming infants or others[2]. The incidence of postpartum depression in patients with pregnancy-induced hypertension is about 9.4%, significantly higher than in non-depressed pregnant women[3]. Women can have both hypertension and depression during pregnancy and puerperium, which are a threat to maternal and infant health. The pathogenesis of postpartum depression is still unknown, and it may be related to genetic, mental, biochemical, social, and other factors. Therefore, it is practical to integrate and evaluate the risk factors for postpartum depression in patients with pregnancy-induced hypertension and to detect high-risk patients as early as possible, which is of guiding effects for the clinical development of personalized prevention programs and prognosis of patients. In this study, by analyzing the risk factors for postpartum depression in patients with pregnancy-induced hypertension, we constructed a personalized nomogram model to provide reference data for reducing the occurrence of clinical postpartum depression.

MATERIALS AND METHODS

Patient data

We conducted a retrospective study on 276 patients with pregnancy-induced hypertension in Huzhou Maternity and Child Health Care Hospital between January 2017 and April 2022. The enrolled patients met the following criteria: Diagnosis of pregnancy-induced hypertension[4]; age ≥ 18 years; and complete clinical data, laboratory examination data, and 5-HT1A receptor gene C (-1019)G [5-HTR1AC(-1019)G] detection data. The exclusion criteria were: Abnormal cognitive function; malignant tumours, myocardial infarction, stroke, or other serious diseases; inability to communicate smoothly with language; or prenatal history of mental illness or family history.

Clinical data collection

We collected the clinical data by consulting the electronic medical records of patients, including gestational weeks of pregnancy-induced hypertension, adverse delivery outcomes, adverse delivery history, family support status, vitamin A deficiency (VAD) during pregnancy and puerperium, complications, family history of hypertension, delivery mode, delivery times, education level, planned pregnancy, occupational status during pregnancy and puerperium, feeding mode, 5-HTR1AC(-1019)G, intestinal flora imbalance during pregnancy and puerperium, weight gain during late

pregnancy, age, family monthly income during pregnancy and puerperium, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), hypersensitive C-reactive protein (Hs-CRP), and procalcitonin (PCT).

Definition and detection methods of related indicators

Adverse birth outcomes included premature birth (gestational age < 37 wk), birth defects, low weight, asphyxia, and infection. The family member support score was measured using the social support rating scale developed by Xiao Shuiyuan to evaluate the support of family members (parents, spouses, compatriots, children, and one other). The total score was 4–16 points, divided into four levels: Full strength, general, very little, and no support. The higher the score, the higher the level of family support[5]. In smears of faecal samples taken from patients during pregnancy and puerperium, a large number of suppressed proto-flora, a decrease in the total number of bacteria, an increase in Gram-negative bacteria, or a decrease/increase in Gram-positive bacteria indicated intestinal flora imbalance.

Weight gain in the third trimester was weight in the third trimester minus the initial weight. The boundaries for the classification of pregnant women with normal and overweight initial weight were an insufficient increase, < 11.5 and < 7 kg; sufficient increase, 11.5-16 and 7-11.5 kg; and excess increase, > 16 and > 11.5 kg[6]. At 16 wk of gestation and 6 wk after delivery, the venous peripheral blood serum VA content was determined by HPLC. Serum VA concentration < 0.7 μmol/L was determined as VAD[7]. Complications included thyroid disease, kidney disease, heart disease, and diabetes. The concentration of EPA, DHA, and AA in venous blood serum was determined by the double antibody sandwich method on day 3 after delivery. Hs-CRP and PCT were measured by Roche Cobas 8000C701 biochemical analyzer and Roche E411 Luminescence analyzer, respectively.

Grouping

At 6 wk postpartum, the Edinburgh Postpartum Depression Scale (EPDS)[8] was used to assess depression status. The total score was 0-30 points. The higher the score, the more serious the depression. Patients with EPDS scores ≥ 13 were diagnosed with postpartum depression. Women who met the criteria for postpartum depression fell into the depression group, and the remainder into the non-depression group.

Statistical methods

We analyzed and processed the data using R version 4.0.3 and performed LASSO regression analysis with the glmnet package. We used the rms package to draw the nomogram and calibration curve and the predictive receiver operating characteristic curve (ROC) package to draw the ROC. We verified the resulting nomogram model by bootstrap self-sampling 500 times and evaluated its efficacy by the area under the ROC curve (AUC). The test level was $\alpha = 0.05$.

RESULTS

Comparison of clinical data of patients

Among the 276 patients with pregnancy-induced hypertension, 54 were in the depression group and 222 in the non-depression group. The incidence of postpartum depression in patients with pregnancy-induced hypertension was 19.57% (54/276). We compared the number of gestational weeks, adverse delivery outcomes, family support status, VAD during pregnancy and puerperium, complications, family history of hypertension, maternal intestinal flora imbalance, weight gain in the third trimester, EPA and DHA between the two groups (Table 1).

Multivariate analysis of postpartum depression in pregnancy-induced hypertension

We put independent variables ($P < 0.05$) and dependent variables (grouping, 0 = non-depression group, 1 = depression group) into a multivariate logistic regression analysis model (Table 2). VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy and puerperium, EPA, and DHA were independent risk factors for postpartum depression ($P < 0.05$) (Table 3). The AUC of VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy and puerperium, EPA, and DHA in predicting postpartum depression in patients with pregnancy-induced hypertension were 0.612, 0.584, 0.603, 0.293, and 0.281, respectively. The best cut-off values of EPA and DHA were 1.82 pg/mL and 2.18 pg/mL, respectively. Figure 1A shows the ROC curve of each index to predict postpartum depression in patients with pregnancy-induced hypertension.

Construction of nomogram model

The independent risk factors for postpartum depression in patients with pregnancy-induced hypertension were used as predictors to construct a nomogram model (Figure 2). The internal verification was carried out by bootstrap self-sampling 500 times. The slope of the calibration curve was similar to that of the diagonal line, suggesting that the degree of fitting between the calibration curve and the ideal curve was high, indicating that there was no significant difference between the predicted and measured values. The average absolute error (0.037) was small, which suggested that the nomogram model had a predictive effect (Figure 3).

ROC curve analysis of nomogram model prediction

The AUC predicted by the nomogram for each index was 0.867 greater than the AUC of each index in Figure 1A. The specificity and sensitivity were 0.676 and 0.889, respectively. The Hosmer–Lemeshow test statistic was 10.739, and there was no significant difference between the predicted value and actual ($P = 0.217$) (Figure 1B).

Table 1 Comparison of clinical data of patients with pregnancy-induced hypertension

Variables	Depression group (*n* = 54)	Non-depression group (*n* = 222)	t/χ^2/Z	*P* value
Gestational weeks of pregnancy-induced hypertension			-2.902	0.004
< 28	20 (37.04)	58 (26.13)		
28–34	30 (55.56)	100 (45.05)		
> 34	4 (7.41)	64 (28.83)		
Adverse birth outcomes			16.283	< 0.001
Yes	16 (29.63)	20 (9.01)		
No	38 (70.37)	202 (90.99)		
History of adverse childbirth			0.310	0.578
Yes	8 (14.81)	40 (18.02)		
No	46 (85.19)	182 (81.98)		
Family support status			-3.349	0.001
Very little or no support	6 (11.11)	4 (1.80)		
General support	26 (48.15)	78 (35.14)		
Full support	22 (40.74)	140 (63.06)		
VAD during pregnancy and puerperium			29.504	< 0.001
Yes	14 (25.93)	8 (3.60)		
No	40 (74.07)	214 (96.40)		
Complications			12.325	< 0.001
Yes	28 (51.85)	60 (27.03)		
No	26 (48.15)	162 (72.97)		
Asthma during pregnancy			3.140	0.076
Yes	10 (18.52)	22 (9.91)		
No	44 (81.48)	200 (90.09)		
Family history of hypertension			15.471	< 0.001
Yes	12 (22.22)	12 (5.41)		
No	42 (77.78)	210 (94.59)		
Mode of delivery			-0.285	0.775
Cesarean section	16 (29.63)	74 (33.33)		
Natural birth	32 (59.26)	120 (54.05)		
Vaginal midwifery	6 (11.11)	28 (12.61)		
Number of deliveries (times)			0.591	0.442
1 (primiparous)	32 (59.26)	144 (64.86)		
≥ 2 (multiparous)	22 (40.74)	78 (35.14)		
Education level			-1.490	0.136
High school and below	18 (33.33)	52 (23.42)		
Junior college	24 (44.44)	106 (47.75)		
Bachelor's degree and above	12 (22.22)	64 (28.83)		
Plan a pregnancy			0.409	0.522
No	10 (18.52)	50 (22.52)		

Yes	44 (81.48)	172 (77.48)		
Occupational status during pregnancy			-0.459	0.646
Not in office	10 (18.52)	50 (22.52)		
Intermittent rest	32 (59.26)	124 (55.86)		
On-the-job	12 (22.22)	48 (21.62)		
Feeding methods			-0.180	0.857
Artificial feeding	10 (18.52)	46 (20.72)		
Mixed feeding	24 (44.44)	94 (42.34)		
Pure breastfeeding	20 (37.04)	82 (36.94)		
5-HTR1AC (-1019) G				
Genotype			-1.269	0.205
GG	30 (55.56)	117 (52.70)		
CG	12 (22.22)	17 (7.66)		
CC	12 (22.22)	88 (39.64)		
Allelic			3.676	0.055
G	72 (66.67)	251 (56.63)		
C	36 (33.33)	193 (43.47)		
Intestinal flora imbalance during pregnancy and childbirth			16.283	< 0.001
Yes	16 (29.63)	20 (9.01)		
No	38 (70.37)	202 (90.99)		
Weight gain in late pregnancy			-2.122	0.034
Increase excess	22 (40.74)	44 (19.82)		
Insufficient increase	12 (22.22)	80 (36.04)		
Adequate increase	20 (37.04)	98 (44.14)		
Age (years)	33.25 ± 9.46	32.87 ± 10.64	0.240	0.810
Maternal family monthly income (yuan)	3766.15 ± 1348.26	4200.85 ± 1622.26	1.821	0.070
EPA (pg/mL)	1.75 ± 0.31	2.02 ± 0.33	7.475	< 0.001
DHA (pg/mL)	1.83 ± 0.27	2.08 ± 0.36	4.784	< 0.001
AA (lgx, pg/mL)	1.08 ± 0.25	0.98 ± 0.36	1.930	0.055
Hs-CRP (mg/L)	21.57 ± 5.39	22.04 ± 5.12	0.599	0.550
PCT (μg/L)	2.02 ± 0.59	1.95 ± 0.46	0.946	0.345

VAD: Vitamin A deficiency; 5-HTR1AC(-1019)G: 5-HT1A receptor gene C(-1019)G; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; AA: Arachidonic acid; hs-CRP: High-sensitivity C-reactive protein; PCT: Procalcitonin.

DISCUSSION

Postpartum depression in patients with pregnancy-induced hypertension can cause neurological and endocrine system disorders, often making them lose their ability to care for themselves and their infants, which is not conducive to them and their infant's health[9]. Other studies have shown that for infants aged 1.5-2 mo, maternal postpartum depression may lead to developmental delays in gross motor, fine motor, and communication areas. Research has suggested that postpartum depression harms mothers and adversely affects children's cognition, behaviour, temperament, and physical development[10]. The risk of postpartum depression in patients with pregnancy-induced hypertension is higher than that in normal pregnant, which may be related to many factors such as VAD during pregnancy and puerperium, family history of hypertension, and intestinal flora imbalance during pregnancy and puerperium. Therefore, integrating the risk factors for postpartum depression in patients with pregnancy-induced hypertension is of clinical significance for identifying high-risk patients.

Table 2 Assignment

Variable	Assignment
Gestational weeks of pregnancy-induced hypertension	0 > 34; 1, 28–34; 2 < 28.
Adverse birth outcomes	0 = No, 1 = Yes
Family support status	0 = full support, 1 = general support, 2 = little or no support
VAD during pregnancy and puerperium	0 = No, 1 = Yes
Complications	0 = none, 1 = have
Family history of hypertension	0 = none, 1 = have
Intestinal flora imbalance during pregnancy and childbirth	0 = none, 1 = have
Weight gain in late pregnancy	0 = increase sufficient, 1 = increase insufficient, 2 = increase excessive
EPA	Actual value
DHA	Actual value

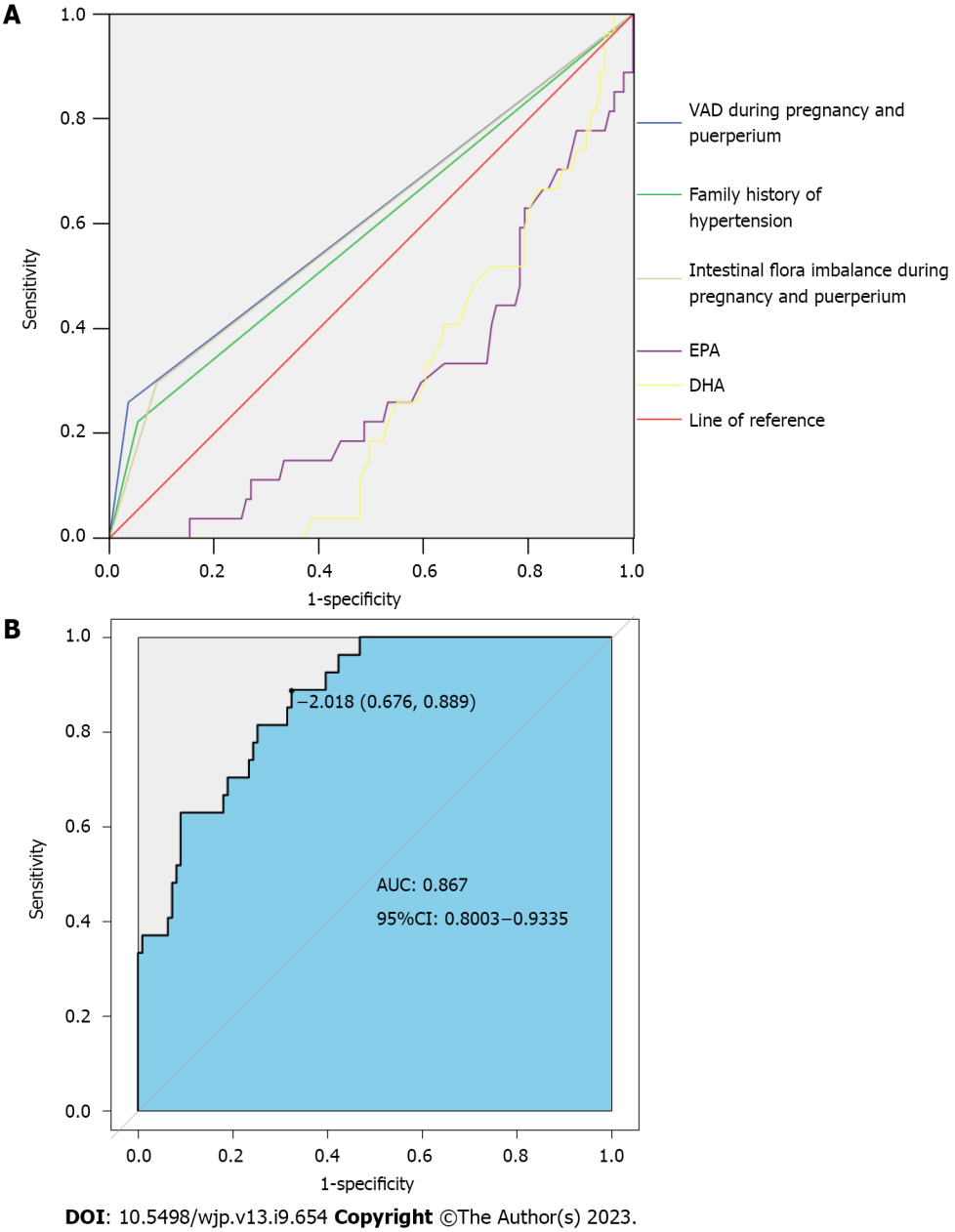
VAD: Vitamin A deficiency; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

Table 3 Multivariate logistic regression analysis of postpartum depression in patients with pregnancy-induced hypertension

Independent variable	*B*	Wald	SE	*P* value	OR (95%CI)
Gestational weeks of pregnancy-induced hypertension	-	-	4.062	0.131	-
No. of weeks of pregnancy (1)	-1.564	0.816	3.678	0.055	0.209 (0.042–1.035)
Gestational weeks of pregnancy-induced hypertension (2)	-0.592	0.457	1.677	0.195	0.553 (0.226–1.355)
Adverse birth outcomes	0.261	0.684	0.145	0.703	1.298 (0.340–4.959)
Family support status	-	-	1.545	0.462	-
Family support status (1)	-1.365	1.155	1.397	0.237	0.255 (0.027–2.456)
Family support status (2)	-0.630	0.898	0.492	0.483	0.533 (0.092–3.095)
VAD during pregnancy and puerperium	2.159	0.642	11.296	0.001	8.662 (2.459–30.506)
Complications	-0.526	0.73	0.520	0.471	0.591 (0.141–2.470)
Family history of hypertension	1.868	0.675	7.667	0.006	6.474 (1.726–24.289)
Intestinal flora imbalance during pregnancy and childbirth	1.877	0.559	11.273	0.001	6.535 (2.185–19.551)
Weight gain in late pregnancy	-	-	4.060	0.131	-
Weight gain in late pregnancy (1)	-0.977	0.490	3.980	0.046	0.377 (0.144–0.983)
Weight gain in late pregnancy (2)	-0.359	0.538	0.446	0.504	0.698 (0.243–2.003)
EPA	-3.125	0.780	16.04	< 0.001	0.044 (0.010–0.203)
DHA	-2.568	0.644	15.88	< 0.001	0.077 (0.022–0.271)

VAD: Vitamin A deficiency; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

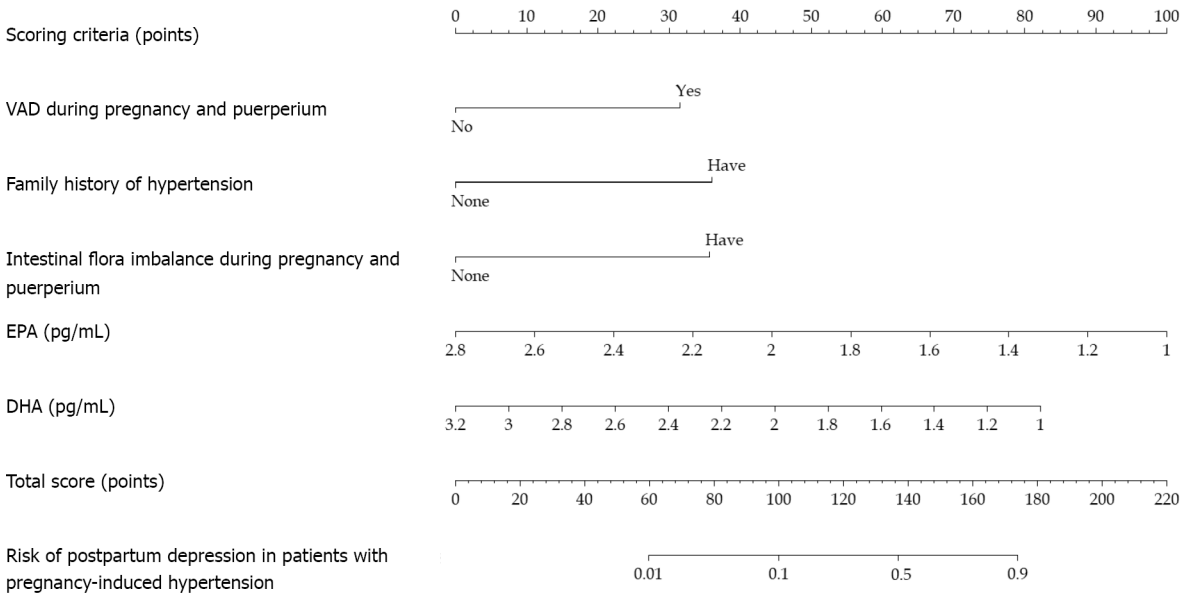
The postpartum depression incidence in 138 patients with pregnancy-induced hypertension was 19.57%, similar to previous studies[11]. Multivariate logistic regression analysis showed that patients with pregnancy-induced hypertension and VAD during pregnancy and puerperium, family history of hypertension, maternal intestinal flora imbalance, low EPA level, or low DHA level had an increased risk of postpartum depression. We speculated that progesterone level in pregnant women in early pregnancy decreases. Because progesterone can promote the release of VA stored in the liver and adipose tissue into blood, this function of progesterone is weakened after progesterone deficiency, resulting in a decrease in serum VA concentration and the development of VAD. VAD during puerperium may also be related to insufficient progesterone secretion. Long-term continuous VAD during pregnancy and puerperium can promote postpartum depression[12]. In the present study, the proportion of VAD during pregnancy and puerperium in depressed patients was higher than in non-depressed patients, indicating that perinatal VAD also increased the risk of postpartum depression in patients with pregnancy-induced hypertension. There is no consensus on the mechanism of VAD in



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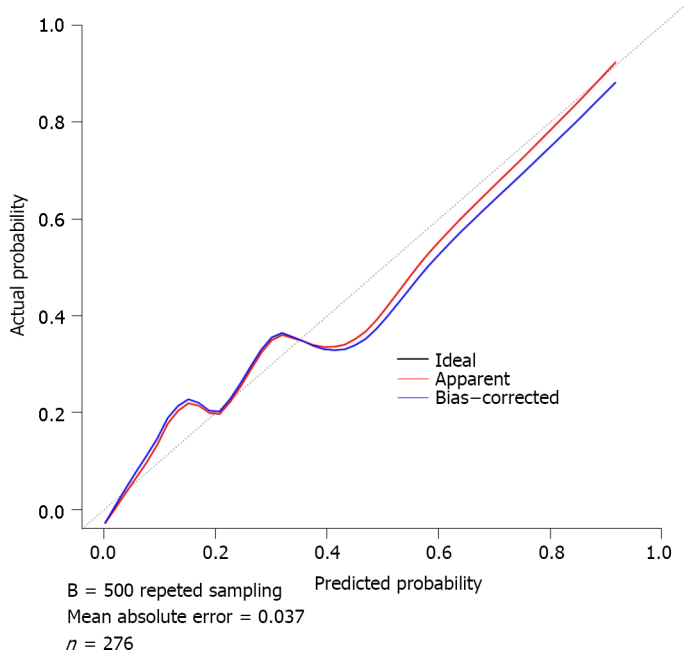
Figure 1 Receiver operating characteristic curve. A: each index in predicting postpartum depression in patients with pregnancy-induced hypertension; B: The graph model predicting the risk of postpartum depression in pregnancy-induced hypertension. EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

postpartum depression development. Some scholars believe that VA can affect the proliferation and differentiation of nerve cells, synapse formation, and axon growth. Studies have also found that VAD may be the basis of the pathogenesis of Alzheimer's disease, which can increase hippocampal Aβ deposition, resulting in hippocampal plasticity and memory function[13]. Therefore, VA is involved in related activities of cranial nerves. These activities may be factors that maintain a good mood. Once the body has continuous VAD, it may increase the incidence of depression. For pregnancy-induced hypertension patients with a family history of hypertension, the psychological burden may be aggravated by similar diseases in their relatives, resulting in anxiety, such as poor pregnancy and poor fetal birth due to unsatisfactory blood pressure control, so it is more likely to induce postpartum depression. Research has also shown a significant difference in the family history of hypertension between the postpartum depression group and the non-depression group of pregnant women with gestational hypertension[14], which is consistent with the results of our study. In recent years, more studies on the mechanism of postpartum depression have shifted from social environmental factors to biological factors (such as gene polymorphism). Abnormal intestinal flora structure can cause abnormal fluctuations in the central nervous system, thus promoting the occurrence of mental diseases such as depression. Intestinal flora imbalance can induce an immune response, and then the hypothalamus-pituitary-adrenal (HPA) axis is abnormally active, and depression occurs. Relevant studies have also shown that after bifidobacteria supplementation to people with intestinal flora imbalance, the HPA axis activity weakens. Also, the concentration of neurotrophic factors in the brain that regulate neuronal development increases, and the HPA axis improves[15]. Therefore, intestinal flora imbalance is a risk factor for postpartum depression in patients with pregnancy-induced hypertension. Clinically, we can reduce the occurrence of postpartum depression by



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Figure 2 Nomogram model of postpartum depression in patients with pregnancy-induced hypertension. EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.



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Figure 3 Correction curve.

improving the composition of intestinal flora in patients with pregnancy-induced hypertension. EPA and DHA are fatty acids with multiple double bonds and are chief components of phospholipids in the human brain. Phospholipids ensure the integrity and fluidity of nerve cell membranes and participate in the signal transduction of various substances in nerve cells. Therefore, EPA and DHA are closely related to the brain's nervous system. The lack of both may cause neurological and psychological disorders and damage the cerebellum, vision, and cognition. The lower the level of EPA or DHA, the more prone patients are to depression. Serum EPA and DHA levels affect the formation of postpartum depression and negative correlation[16,17]. These show that ensuring adequate EPA or DHA intake during pregnancy may be a protective factor for postpartum depression in patients with pregnancy-induced hypertension. This study also analyzed the 5-HTR1AC (-1019) G genotype and allele in patients with pregnancy-induced hypertension. The results showed that there was no difference in the gene polymorphism of this locus between patients with postpartum depression and non-depressed patients, which was inconsistent with relevant research[18]. It may be related to the

different sample sizes and inclusion/exclusion criteria of the two studies. Therefore, we speculated that the occurrence of postpartum depression in patients with pregnancy-induced hypertension may be slightly influenced by biological factors.

This study summarized the risk factors related to postpartum depression in patients with pregnancy-induced hypertension and applied these five risk factors as predictive variables to construct a predictive nomogram model. After the model verification, we found that the degree of fitting between the calibration and the ideal curve was high. The AUC predicted by the nomogram model was higher, indicating that the model had better discriminant ability. The Hosmer–Lemeshow test showed that the predictive data of the model were not much different from the actual data, suggesting that the model had high calibration or predictive accuracy. The nomogram model showed the relationship between the five variables of VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy and puerperium, EPA, and DHA with the calibrated lines, which was readable and easy to evaluate. This study explored the nomogram model of postpartum depression in post-inflammatory hyperpigmentation (PIH) patients, which can help clinicians quickly and accurately identify patients with PIH who are at risk of depression after high production, help guide them to take targeted intervention measures, and thus reduce the possibility of postpartum depression in patients. It has high clinical application value.

There were some limitations to this study. All the women were from a single centre, and there may have been potential selection bias. The risk prediction nomogram model for postpartum depression in patients with pregnancy-induced hypertension was only internally validated, and there was a lack of external validation from other central data. Therefore, we need sufficient external evidence before the practical application of the model.

CONCLUSION

Postpartum depression in patients with pregnancy-induced hypertension is affected by VAD during pregnancy and puerperium, family history of hypertension, intestinal flora imbalance during pregnancy, and puerperium, EPA, and DHA. The established nomogram model can effectively assess its risk.

ARTICLE HIGHLIGHTS

Research background

The clinical prediction of postpartum depression in patients with pregnancy-induced hypertension is still insufficient, and the application of the nomogram model in predicting postpartum depression in patients with pregnancy-induced hypertension is rarely reported.

Research motivation

Compared with normal pregnant, pregnancy-induced hypertension patients have a higher risk of postpartum depression, which is related to several factors. By integrating risk factors of postpartum depression in pregnancy-induced hypertension and constructing predictive models, this study guides identifying high-risk patients and early clinical intervention.

Research objectives

The study's purpose was to integrate the risk factors of postpartum depression in patients with pregnancy-induced hypertension, construct a graph prediction model, and evaluate the predictive effect of the model.

Research methods

Multivariate logistic regression analysis and LASSO regression were used to analyze the factors related to postpartum depression in pregnancy-induced hypertension. R version 4.0.3 was used to construct a line graph risk predictive model. The area under the receiver operating curve was used to evaluate effectiveness.

Research results

Vitamin A deficiency (VAD) during pregnancy and puerperium, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are independent risk factors for postpartum depression in pregnancy-induced hypertension. The histogram model established by this method had good predictive efficacy and could guide clinical prevention and intervention.

Research conclusions

Postpartum depression in pregnancy-induced hypertension is related to VAD during pregnancy and puerperium, family history of hypertension, intestinal flora disorders during pregnancy and perinatal period, EPA, and DHA. The predictive efficacy of the risk model established by this method has clinical application value.

Research perspectives

Future research directions should increase the sample size or multicenter study to verify the results, enhance the reliability of the conclusions, and better carry out clinical prevention interventions.

FOOTNOTES

Author contributions: Pan JW designed and performed the research and wrote the paper; Zhao G designed the research and supervised the report.

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Retrospective Study

Immune function, gastrointestinal hormone levels, and their clinical significance in patients with gastric ulcers complicated with depression

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Abstract

BACKGROUND

Gastric ulcer (GU) is a common digestive tract disease, and medical records of GU combined with depression are increasingly common. Currently, the risk factors and pathogenesis of GU complicated with depression remain unclear. Low immune function and gastrointestinal hormone levels may also be significant risk factors. Therefore, this study explored the immune function and gastrointestinal hormone levels in patients with GU combined with depression.

AIM

To explore the immune function, gastrointestinal hormone level, and clinical significance of patients with GU combined with depression.

METHODS

A retrospective analysis was conducted on 300 patients with GU combined with depression admitted to Guizhou Provincial People's Hospital from January 2021 to June 2022 as the study subjects. According to the Hamilton Depression Scale (HAMD) score, patients were divided into mild-to-moderate (n = 210) and heavy (n = 90) groups. Basic data, immune function indices [immunoglobulin A (IgA), IgM, IgG, serum $CD4^+$ and $CD8^+$ percentage, and $CD4^+/CD8^+$ ratio], and gastrointestinal hormone indices [serum gastrin (GAS), cholecystokinin (CCK), and motilin (MTL) levels] were collected. The basic data of the two groups were compared, and the immune function and gastrointestinal hormone indices were analyzed. Multivariate logistic regression was used to analyze the factors influen-

cing the severity of GU complicated with depression. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to analyze the value of the immune function index, gastrointestinal hormone index, and combined index in predicting the severity of GU complicated with depression.

RESULTS

There were no marked differences in sex, age, body mass index, abdominal distension, abdominal pain, belching, nausea, vomiting, or sleep disorders between the heavy and mild-to-moderate groups ($P > 0.05$). There was a marked difference in the family history of depression between the heavy and mild-to-moderate groups ($P < 0.05$). There were significant differences in serum IgA and IgM levels and serum $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios between the heavy and mild-to-moderate groups ($P < 0.05$). Multivariate analysis showed that IgA, IgM, GAS, and CCK serum levels influenced the severity of GU with depression ($P < 0.05$). The AUC of the ROC curve for serum IgA level predicting GU with depression severity was 0.808 [95% confidence interval (CI): 0.760-0.857], the AUC of the serum IgM level was 0.757 (95%CI: 0.700-0.814), the AUC of the serum GAS level was 0.853 (95%CI: 0.810-0.897), the AUC of the serum CCK level was 0.762 (95%CI: 0.709-0.822), the AUC of immune function (IgA, IgM) and gastrointestinal hormone levels (GAS, CCK) for the prediction of GU with depression severity was 0.958 (95%CI: 0.933-0.976).

CONCLUSION

Important factors influencing GU complicated with depression are serum IgA, IgM, GAS, and CCK indicators. They can be used as indicators to predict the severity of GU complicated with depression.

Key Words: Gastric ulcer combined with depression; Immune function; Gastrointestinal hormones

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Core Tip: The occurrence and severity of gastric ulcer (GU) combined with depression may be related to autoimmune dysfunction and gastrointestinal hormone levels. In this study, multivariate logistic regression analysis was used to influence the severity of concurrent depression in GU. The results suggest that impaired T cell function and gastrointestinal hormone disorders may directly affect the development and development of depression. In addition, the immune function indicators combined with gastrointestinal hormone levels predict high AUC, specificity and sensitivity, which has a very good reference value.

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INTRODUCTION

With the continuous development of living standards, people's eating and living habits have changed to varying degrees; however, poor living habits have had a greater impact on people's health. Gastric ulcers (GU) are common digestive system diseases. The occurrence and continuous progression of the disease are related to the dynamic balance between gastric mucosal defense and invasion factors. *Helicobacter pylori* (*H. pylori*) infection, excessive gastric acid secretion, and adverse drug factors are all influencing factors that cause GU[1,2]. Gastric juice concentration in patients with GU stimulates the gastric mucosa, promotes changes in the gastric structure and environment, causes serious damage to the gastric mucosa, and causes long-term stay of pathogenic factors, resulting in the long-term treatment of the disease[3]. Clinical manifestations of GU include stomach and abdominal pain, heartburn, acid reflux, among others. The symptoms worsen after eating irritating foods or foods that are hard to digest. Smoking and alcohol consumption can also cause GU. Patients with severe GU often experience gastric perforation and gastric bleeding[4].

Recently, psychophysiological factors have been significant in the pathogenesis of gastrointestinal illnesses. GU are characterized by repeated attacks that can easily cause adverse severe psychological states. Some patients also experience anxiety and depression due to a lack of timely and effective treatment for physical illness, which makes depression increasingly prominent in GU patients[5]. Anti-*H. pylori* therapy, drugs controlling excessive gastric acid secretion, and protecting gastric mucosa are primarily used for the clinical treatment of GU. The impact of psychological factors on disease occurrence and progression in clinical practice is often overlooked, which makes it difficult to treat patients comprehensively[6]. Relevant data show that poor psychological status may increase the risk of digestive disorders[7]; however, there are few studies on patients with GU associated with depression. Exploring the factors influencing GU combined with depression is important for clinical treatment and the improvement of patients' quality of life. Studies have shown that the occurrence of GU combined with depression may be related to abnormal autoimmune function and disorders of gastrointestinal hormone levels[8]; however, the specific mechanism is not clear. Due to the decrease in gas-

trointestinal function and food intake, GU complicated with depression is often accompanied by a decline in immune function, and the adverse psychological state aggravates the risk of malnutrition. The intestinal mucosal barrier and immune function are extremely poor, which increases the risk of depression. Therefore, 300 patients with GU and depression were included in this study to explore their immune function, gastrointestinal hormone levels, and clinical significance, to provide a reference for reducing the incidence of GU complicated by depression.

MATERIALS AND METHODS

Patient characteristics

A retrospective analysis was conducted to select 300 patients with GU complicated with depression admitted to Guizhou Provincial People's Hospital from January 2021 to June 2022 as the study subjects. Inclusion criteria: (1) Age ≥ 18 years old; (2) All patients have nausea, stomach pain, and acid reflux symptoms; and (3) The basic information and laboratory indicators of all patients are complete. The exclusion criteria were as follows: (1) Patients with malignant tumors or chronic atrophic gastritis and other gastrointestinal illnesses; (2) Patients who had undergone gastrointestinal surgery in the past 3 mo; (3) Patients with organic disorders; and (4) Patients with autoimmune diseases and systemic inflammatory diseases.

Diagnostic criteria for GU[9]: GU was confirmed by endoscopy, and the pathological diagnosis of *H. pylori* infection was positive. Diagnostic criteria for depression[10]: Diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders were employed. The diagnosis was based on the patient's low mood, slow thinking, reduced language, movements, suspected illness, insomnia, loss of interest, and related symptoms lasting more than 2 wk. The severity of the disease and the degree of social function impairment increase with the number of symptoms.

Grouping method

All patients on the day of admission, patients were routinely assessed using the Hamilton Depression Scale (HAMD)[11], And were graded according to the HAMD scale: A score of 7 points indicates no depression, > 8-19 points indicates depression, > 20-34 points indicates mild to moderate depression, and > 35 points indicates major depression. All enrolled patients with GU and depression were divided into mild-to-moderate (n = 210) and heavy (n = 90) groups.

Clinical data collection

Clinical data collection: (1) Basic information: Sex, age, body mass index (BMI), abdominal distension, abdominal pain, belching, nausea, vomiting, sleep disorders, and family history of depression; (2) Immune function index: The levels of serum immunoglobulin A (IgA), IgM, and IgG were detected by immunoturbidimetry (the kit was purchased from Lifotronic Technology Co., Ltd.). The percentages of serum $CD4^+$ and $CD8^+$ cells were detected using a Beckman CytoFLEX flow cytometer and a supporting kit (Beckman Coulter), and the ratio of $CD4^+/CD8^+$ cells was calculated; and (3) Gastrointestinal hormone indices: The levels of serum gastrin (GAS), cholecystokinin (CCK), and motilin (MTL) were detected by ELISA (the kit was purchased from MLBIO Enzyme Linked Biology).

Statistical analysis

Data analysis was performed using SPSS statistical software 24.0. The measurement data conforming to the normal distribution were expressed as mean ± SD and analyzed by t-test. Count data is expressed as frequency percentage (n%) by the χ^2 test. Multivariate logistic regression analysis was used to explore factors influencing the severity of GU complicated with depression. The receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were used to analyze the value of the immune function index, gastrointestinal hormone index, and combined index in predicting the severity of GU complicated with depression, and the specificity and sensitivity were calculated. Test level: α = 0.05.

RESULTS

Basic data analysis

Figure 1 shows the number of patients, the number of patient inclusion, and the flow chart of the analysis method. There was no significant difference in gender, age, BMI, abdominal distension, abdominal pain, belching, nausea, vomiting, and sleep disorders between the heavy group and the mild to moderate group (P > 0.05). There was statistically significant difference in family history of depression between severe group and mild to moderate group (P < 0.05) (Table 1).

Comparison of the immune function indicators between the two groups

There were significant differences in serum IgA and IgM levels and serum $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ ratios between the heavy and mild-to-moderate groups (P < 0.05). There was no significant difference in serum IgG level between the two groups (P > 0.05) (Table 2).

Comparison of the gastrointestinal hormone indexes

Serum GAS and CCK levels were compared between the severe and mild-to-moderate groups (P < 0.05), and there was no difference in serum MTL levels between the two groups (P > 0.05) (Table 3).

Table 1 Comparison of general data [*n* (%), mean ± SD]

Feature	Heavy group (*n* = 90)	Mild to moderate group (*n* = 210)	χ^2/t value	*P* value
Gender (male/female)	48/42	109/101	0.052	0.820
Age (yr)	45.29 ± 4.56	46.37 ± 5.44	-1.773	0.078
BMI (kg/m^2)	22.48 ± 2.17	22.19 ± 2.13	1.114	0.266
Abdominal distension (Yes/No)	51/39	102/108	1.652	0.199
Abdominal pain (Yes/No)	43/47	100/110	0.001	0.980
Belching (Yes/No)	40/50	107/103	1.068	0.301
Nausea (Yes/No)	38/52	98/112	0.502	0.479
Vomiting (Yes/No)	46/44	105/105		
Sleep disorder (Yes/No)	47/43	85/125	3.528	0.060
Family history of depression (Yes/No)	45/45	48/162	21.699	< 0.001

BMI: Body mass index.

Table 2 Comparison of immune function indicators between the two groups (mean ± SD)

Index	Heavy group (*n* = 90)	Mild to moderate group (*n* = 210)	*T* value	*P* value
IgA (g/L)	1.86 ± 0.42	2.54 ± 0.63	-10.791	< 0.001
IgM (g/L)	2.97 ± 0.62	3.59 ± 0.65	-7.698	< 0.001
IgG (g/L)	15.37 ± 3.48	15.42 ± 3.52	-0.113	0.910
$CD4^+$ (%)	32.16 ± 5.31	38.48 ± 5.49	-9.218	< 0.001
$CD8^+$ (%)	29.37 ± 3.52	23.59 ± 3.13	6.800	< 0.001
$CD4^+/CD8^+$ ratio	1.24 ± 0.27	1.67 ± 0.36	-11.104	< 0.001

IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G.

Table 3 Comparison of gastrointestinal hormone indexes between the two groups (mean ± SD)

Group	*n*	GAS (pg/mL)	CCK (ng/L)	MTL (pg/mL)
Heavy group	90	43.52 ± 5.79	154.49 ± 11.68	256.28 ± 13.12
Mild to moderate group	210	52.44 ± 6.23	167.25 ± 13.54	258.18 ± 20.47
t value		-11.598	-7.781	-0.960
P value		< 0.001	< 0.001	0.338

GAS: Gastrin; CCK: Cholecystokinin; MTL: Motilin.

Multivariate analysis affecting the severity of GU combined with depression

The above statistically significant indicators (family history of depression, IgA, IgM, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio, GAS, and CCK) were used as independent variables, and GU combined with depression severity as the dependent variable (see Table 4). Multivariate analysis showed that serum IgA, IgM, GAS, and CCK levels influenced the severity of GU complicated with depression ($P < 0.05$) (Table 5).

ROC curve of immune function predicting GU with depression severity

The AUC of the ROC curve of serum IgA level for predicting GU with depression severity was 0.808 [95% confidence interval (CI): 0.760-0.857], sensitivity was 0.738, and specificity was 0.778, The AUC of the serum IgM level was 0.757 (95%CI: 0.700-0.814), with a sensitivity of 0.748 and a specificity of 0.700 (Figure 2A).

Table 4 The assignments of related indicators

Index	Code	Description of valuation
Family history of depression	X1	1 = Yes; 0 = No
IgA	X2	Enter actual value
IgM	X3	Enter actual value
$CD4^+$	X4	Enter actual value
$CD8^+$	X5	Enter actual value
$CD4^+/CD8^+$ ratio	X6	Enter actual value
GAS	X7	Enter actual value
CCK	X8	Enter actual value

IgA: Immunoglobulin A; IgM: Immunoglobulin M; GAS: Gastrin; CCK: Cholecystokinin.

Table 5 Multi-factor analysis

Index	β	SE	Wald χ^2	*P* value	OR (95%CI)
Family history of depression	0.744	0.551	1.822	1.770	2.103 (0.714-6.193)
IgA	-2.703	0.600	20.313	< 0.001	0.067 (0.021-0.217)
IgM	-1.509	0.487	9.586	0.002	0.221 (0.085-0.575)
$CD4^+$	0.151	0.218	0.482	0.488	1.163 (0.759-1.782)
$CD8^+$	-0.286	0.290	0.969	0.325	0.751 (0.425-1.327)
$CD4^+/CD8^+$ ratio	-9.136	5.432	12.829	0.093	0.000 (0.000-4.525)
GAS	0.267	0.050	28.147	< 0.001	0.766 (0.694-0.845)
CCK	0.093	0.024	15.137	< 0.001	0.911 (0.869-0.955)
Constant	52.073	10.637	23.963	< 0.001	-

IgA: Immunoglobulin A; IgM: Immunoglobulin M; GAS: Gastrin; CCK: Cholecystokinin; OR: Odds ratio; CI: Confidence interval.

The ROC curve of gastrointestinal hormones in predicting GU combined with depression severity

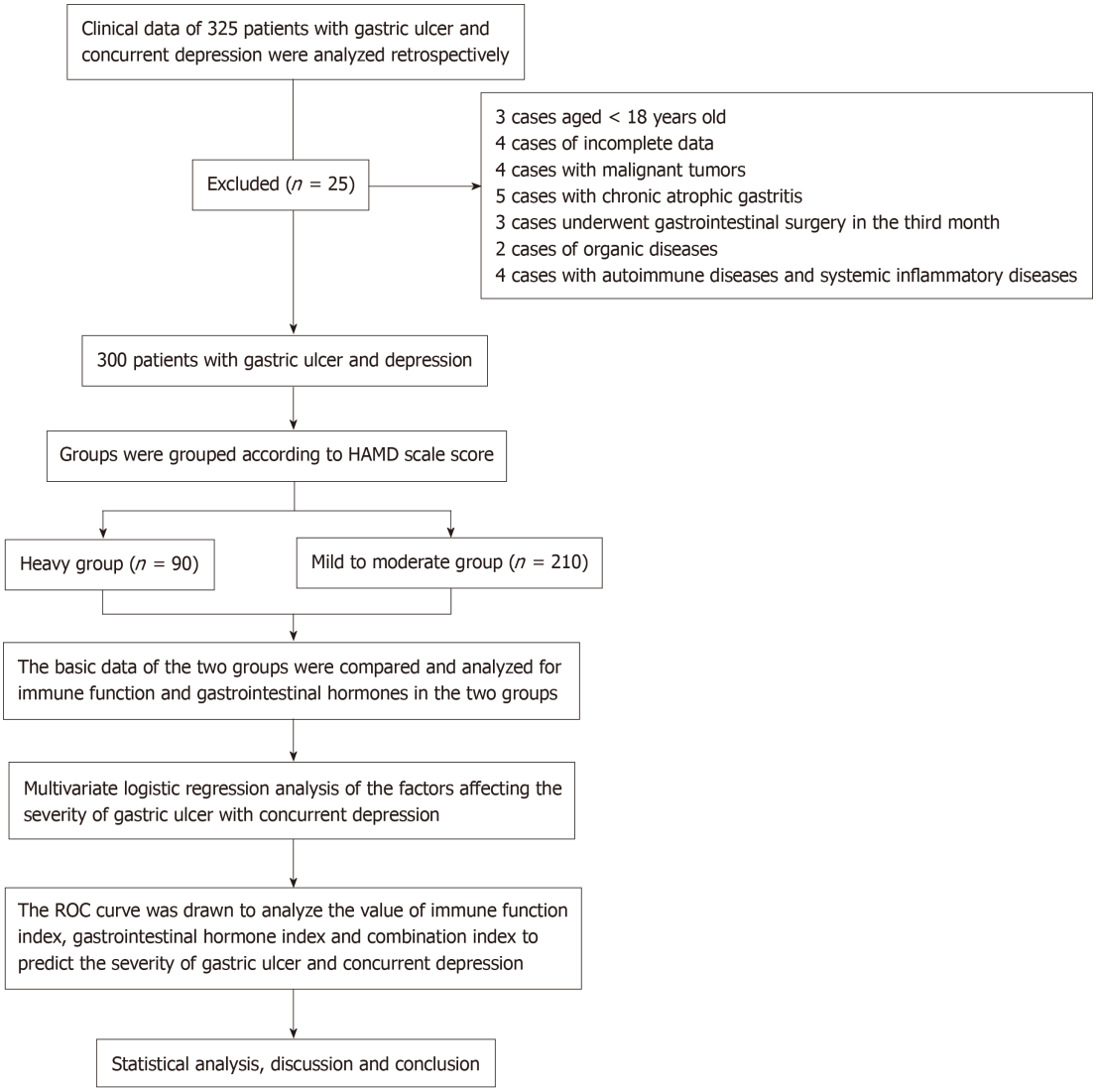
The AUC of the ROC curve of serum GAS level predicting GU with depression severity was 0.853 (95%CI: 0.810-0.897), sensitivity was 0.814, and specificity was 0.767, The AUC of serum CCK level was 0.762 (95%CI: 0.709-0.822), with a sensitivity of 0.590 and a specificity of 0.844 (Figure 2B).

ROC curve of immune function combined with gastrointestinal hormone levels in predicting GU combined with depression severity

The AUC of immune function (IgA, IgM) combined with gastrointestinal hormone levels (GAS, CCK) predicting GU with depression severity was 0.958 (95%CI: 0.933-0.976), sensitivity was 0.967, and specificity was 0.829 (Figure 2C).

DISCUSSION

GU refers to the ulcer formed in the gastric angle, gastric antrum, cardia, and hiatal hernia. It is a gastric mucosal injury that is caused by various factors. It can be caused by *H. pylori* infection, drugs, heredity, diet, and other factors and is often accompanied by acid reflux, belching, abdominal distension, and upper abdominal pain symptoms[12]. The related study showed that the occurrence of GU is caused by the process of 'attack factor' or the weakening of 'defense factor'; the "attack factor" includes gastric acid, pepsin, *H. pylori*, among others, and the "defense factor" includes gastric mucosa, gastric mucus, bicarbonate, among others[13]. It has been found that *H. pylori* infection is the most common cause of GU. *H. pylori* can damage the protective layer of the gastric mucosa, thus accelerating the occurrence of gastric mucosal lesions, easily causing various complications, and threatening the physical and mental health of patients[14]. GU combined with depression is a typical digestive tract illness in clinical medicine, and gastric acid secretion in the human body is associated with psychological pressure. Patients are affected by psychological and physiological factors, and inner



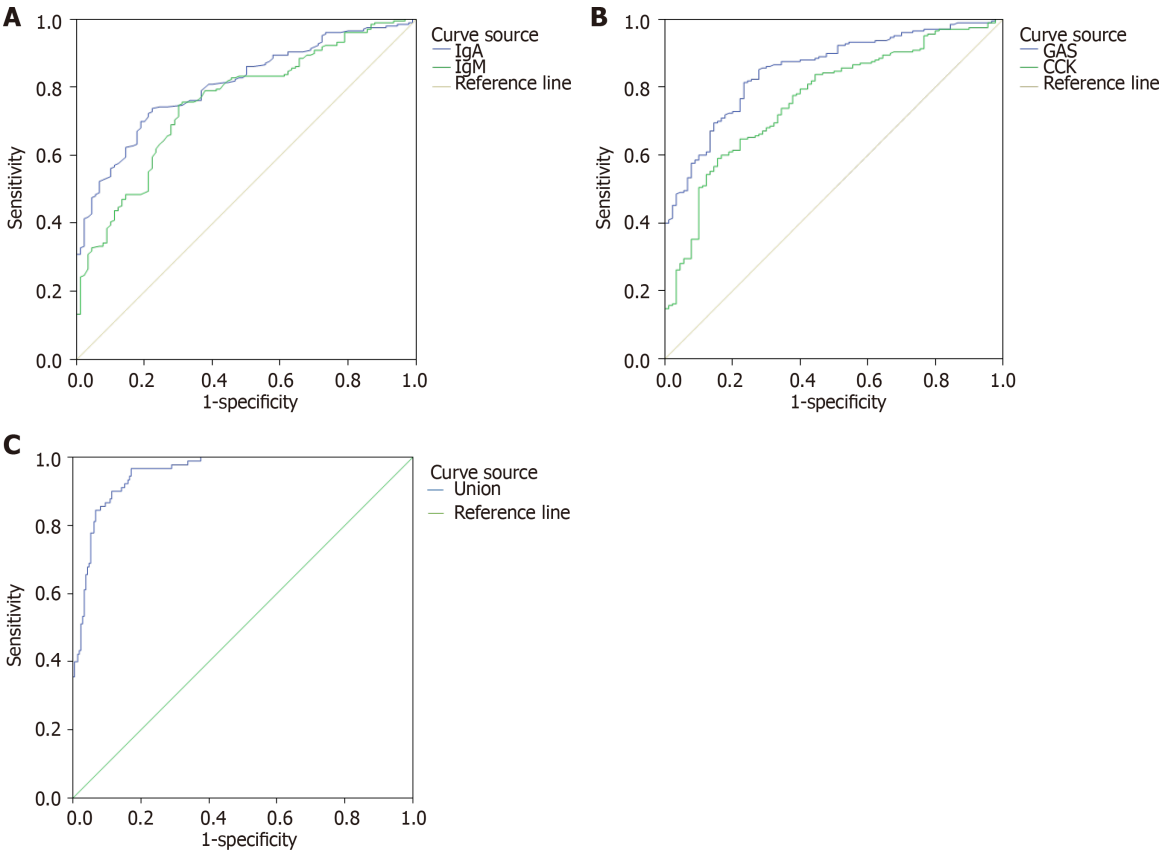
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Figure 1 The number of patients, the number of patients included, and the flow chart of the analysis method. HAMD: Hamilton Depression Scale; ROC: Receiver operating characteristic.

tension and nervous system pressure can cause GUs. The incidence of psychosocial abnormalities has increased in recent years and exists as a comorbidity of other basic and chronic diseases, with these two factors influencing each other[15].

Depression is a primary emotional and common mood disorder. Its incidence ranks second in the incidence of various diseases worldwide. Furthermore, it is found that patients with various chronic diseases have anxiety and depression, and the mortality rate of patients with heart disease complicated with depression is higher than that of patients with simple depression, so the treatment of patients with depression is necessary[16]. The National Institute of Mental Health showed that the prevalence of mental disorders in patients with somatic diseases is as high as 41%[17]. Therefore, while paying clinical attention to the diagnosis and treatment of physical diseases, we should also pay attention to mental and psychological interventions, as the number of patients with GU complicated with depression in China has increased annually[18]. Several factors affect the pathogenesis of GU, which is complicated with depression. Autoimmune dysfunction and gastrointestinal hormone disorders may be important factors affecting disease severity; however, this hypothesis remains controversial. Therefore, it is necessary to explore the importance of immune function and gastrointestinal hormone indices in patients with GU or depression.

In this study, all selected patients were scored using the HAMD. Among them, 210 patients with mild to moderate GU complicated with depression, accounting for 70%, and 90 patients in the heavy group, accounting for 30%. Studies have shown that disease characteristics and severity of depression are influenced by a family history of affective disorder[19]. In this study, the mild-to-moderate and heavy groups had a family history of depression. This indicates that patients with a family history of depression may have more severe anhedonia and anxiety symptoms and that these mood disorders can potentially affect immune function and gastrointestinal hormone levels. The pathogenesis of GU is closely associated with immune deficiency[20]. Depression and anxiety can cause digestive system diseases. Long-term mental disorders overstretch the nervous system, leading to gastrointestinal hormone secretion disorders and excessive sensitivity to food stimulation. Patients with GU and depression have weakened gastrointestinal motility, delayed gastric emptying, and



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Figure 2 The receiver operating characteristic curves. A: The receiver operating characteristic (ROC) curves for the predicted immune function; B: ROC curves predicted by gastrointestinal hormone; C: ROC curves of combined prediction, union: Immune function (immunoglobulin A and immunoglobulin M) combined with gastrointestinal hormone levels (gastrin and cholecystokinin). IgA: Immunoglobulin A; IgM: Immunoglobulin M; GAS: Gastrin; CCK: Cholecystokinin.

uncoordinated gastrointestinal motility, causing a series of complex syndromes such as fullness, belching, and abdominal pain[21]. There was no significant difference in gender, age, BMI, abdominal distension, abdominal pain, belching, nausea, vomiting and sleep disorders between the moderate-to-severe group and the mild-to-moderate group in this study, this result may be related to the sample size included in this study. However, these syndromes must be considered clinically.

Immunoglobulin is produced by B lymphocytes as long as it is a specific binding antigen. Serum IgA, IgM, and IgG are important components of the body's immune cell molecules, which can be consumed in large amounts in consumptive diseases, acute inflammation, and malignant tumors, resulting in a decline in immune function[22]. In this study, serum IgA and IgM levels in the moderate and heavy groups were lower than those in the mild and moderate groups, indicating that impaired B cell function and low immune function could aggravate the risk of infection, GU progression, and depression status. According to modern immunology, the clinical manifestations and prognosis of diseases are closely related to the functional status of T lymphocytes[23]. The percentage of serum $CD4^+$ and $CD8^+$ cells and the $CD4^+/CD8^+$ ratio reflect the cellular immune function of the body. The percentage of serum $CD4^+$ cells are helper T lymphocytes, the percentage of serum $CD8^+$ cells are inhibitory T lymphocytes, and the $CD4^+/CD8^+$ ratio is an index to assess immunity, which can reflect the immune status of the body. When the body is stimulated or damaged by stress, the percentage of $CD4^+$ cells decreased rapidly, the percentage of $CD8^+$ cells increased rapidly, the $CD4^+/CD8^+$ cell ratio increased significantly, and the immune function of the body decreases[24]. In this study, serum $CD4^+$ and $CD4^+/CD8^+$ ratios were significantly decreased in the moderate-to-heavy group, and serum $CD8^+$ levels were markedly increased. This indicates that impaired T-cell function may directly lead to the development of depression. Therefore, enhancing immune cell function is of great clinical value for controlling illness progression in patients with GU and depression.

The gastrointestinal hormone level is a sensitive index that reflects the function of the gastric mucosa. It plays an important role in regulating the function of the digestive system and is closely related to digestive system dysfunction [25]. GAS is the main hormone of the digestive tract that affects gastrointestinal transitional compound movement, prolongs gastric emptying time, stimulates the vagus nerve inhibitory fiber, promotes gastric fundus relaxation, and inhibits reflux of bile discharge[26]. When patients with GU are complicated with depression, the patient's body is in an emergency state, and the levels of stress hormones, such as hypothalamus-pituitary-adrenaline, increase, which affects the interaction between the gastrointestinal flora and gastrointestinal mucosa and the shedding of mucosal mast cells, resulting in dyspepsia[27]. In this study, the levels of serum GAS and CCK were markedly increased in the severe group. This shows that increased secretion or synthesis of gastrointestinal hormones occurs in GU patients with severe depression, leading to an imbalance in the gastrointestinal hormone balance. The low levels of GAS and CCK in plasma

affect the normal functioning of their physiological functions and slow down gastrointestinal motility, thus affecting the digestive tract symptoms of patients with depression. CCK is an important hormone that regulates the gallbladder function. Its main functions include promoting bile secretion, destroying the mucosa lining of the digestive tract, preventing gastrointestinal peristalsis, and prolonging gastric emptying[28]. The increase in CCK levels stimulates the hypothalamus and acts on the central nervous system to inhibit appetite, which is also the reason for the loss of appetite in patients with GU and depression.

In this study, the ROC curves of immune function, gastrointestinal hormone levels, and the combined prediction curve of GU and depression severity were drawn. The results showed that the immune function and gastrointestinal hormone indices alone predicted low AUC, specificity, and sensitivity, and the combined prediction had the highest efficacy, indicating that the immune function indices (IgA and IgM) combined with gastrointestinal hormone levels (GAS and CCK) have good efficacy and significance in predicting the severity of GU and depression. Serum IgA, IgM, GAS, and CCK indicators are simple, convenient, economical, effective, and have strong applicability and operability, which is conducive to the development of primary medical institutions.

Limitations of this study: All the selected participants were admitted to our hospital, the reliability may be affected by the limitation of sample size. In the later stages, the sample size can be expanded clinically, a multicenter study can be conducted, and the mechanism of immune function and gastrointestinal hormone levels in GU complicated with depression can be analyzed in depth.

CONCLUSION

In summary, the important influencing factors of GU with depression were serum IgA, IgM, GAS, and CCK indices. Immune function and gastrointestinal hormone levels can be used as effective indicators to predict the severity of GU combined with depression. Clinically, targeted measures should be taken to address these causes and reduce the risk of GU concomitant with depression.

ARTICLE HIGHLIGHTS

Research background

Psychophysiological factors play a significant role in the pathogenesis of gastrointestinal illnesses. Gastric ulcers (GU) are characterized by repeated attacks that can cause adverse severe psychological states. Some patients also experience anxiety and depression due to a lack of timely and effective treatment for physical diseases, which makes depression increasingly prominent in patients with GU.

Research motivation

The relevant risk factors and pathogenesis of GU concomitant with depression have not yet been fully elucidated. The occurrence and severity of GU complicated with depression may be related to autoimmune dysfunction and gastrointestinal hormonal disorders.

Research objectives

This study aimed to investigate the immune function, gastrointestinal hormone levels, and clinical significance of patients with GU combined with depression and to control disease progression in patients with GU complicated with depression.

Research methods

This study used a retrospective approach to analyze two indexes of immune function and gastrointestinal hormones. Furthermore, it explored the factors influencing the severity of GU concurrent depression using multivariate logistic regression analysis.

Research results

Serum immunoglobulin A (IgA), IgM, gastrin (GAS), and cholecystokinin (CCK) levels were the influencing factors affecting the severity of GU combined with depression; the area under the receiver operating characteristic curve of immune function (IgA, IgM) and gastrointestinal hormone levels (GAS, CCK) for the prediction of GU with depression severity was 0.958 (95% confidence interval: 0.933-0.976).

Research conclusions

The occurrence of GU complicated with depression is related to autoimmune dysfunction and disorders of gastrointestinal hormone levels. Immune function and gastrointestinal hormone levels can be used as effective indicators to predict the severity of GU complicated with depression.

Research perspectives

Using a retrospective analysis approach, patients were divided into severe and mild-moderate groups according to the Hamilton Depression Scale. Basic data from both groups, including immune function and gastrointestinal hormone

markers, were used to analyze the factors affecting the severity of GU and concurrent depression. To explore the value of immune function indices, gastrointestinal hormone indices and a combination of indices were used to predict the severity of GU and depression.

FOOTNOTES

Author contributions: Yang YH and Cui DJ co-designed the study, wrote the paper, contributed equally to this work, and are the first co-authors; Yang ZL, Yuan WQ, and Huang B participated in the study and provided clinical recommendations.

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ORIGINAL ARTICLE

Observational Study

Factors influencing spiritual wellbeing among pancreatic ductal adenocarcinoma patients receiving chemotherapy

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Abstract

BACKGROUND

Spiritual wellbeing emphasizes optimistic and positive attitudes while self-regulating negative emotions when coping with stress. However, there have only been a few small studies of spiritual wellbeing of pancreatic ductal adenocarcinoma (PDAC) patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear.

AIM

To identify factors influencing spiritual wellbeing among patients with PDAC receiving chemotherapy.

METHODS

A total of 143 PDAC patients receiving chemotherapy were enrolled from January to December 2022. Patients completed general information questionnaires including: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale (FACIT-Sp-12), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Zung's Self-rating Anxiety Scale (SAS). Independent sample *t*-test, one-way analysis of variance, Pearson's correlation analysis, and multiple linear regression analysis were adopted for statistical analyses. $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

RESULTS

Total spiritual wellbeing (FACIT-Sp-12) score was 32.16 ± 10.06 points, while dimension sub-scores were 10.85 ± 3.76 for faith, 10.55 ± 3.42 for meaning, and 10.76 ± 4.00 for peace. Total spiritual wellbeing score was negatively correlated with SAS score for anxiety and with the symptom domain of EORTC QLC-C30. Conversely, spiritual wellbeing score was positively correlated with global health status and EORTC QLQ-C30 role functioning domain score. Multivariate

regression analysis identified educational level, health insurance category, symptom domain, functional role domain, and global health status as significant independent factors influencing spiritual wellbeing among PDAC patients undergoing chemotherapy (R^2 = 0.502, P < 0.05).

CONCLUSION
Individualized spiritual support is needed for PDAC patients. Health, daily functioning, emotional, cognitive, and social function status should be taken into account to promote implementation of spirituality in nursing practice.

Key Words: Pancreatic ductal adenocarcinoma; Chemotherapy; Spiritual wellbeing; Quality of life; Anxiety

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Core Tip: Identifying the core factors influencing spiritual wellbeing of pancreatic ductal adenocarcinoma (PDAC) patients undergoing chemotherapy and formulating individualized spiritual care regimens can improve quality of life. However, there have only been a few small studies on spiritual wellbeing of PDAC patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear. In this study, we analyzed factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy, the newest study of PDAC patients undergoing chemotherapy in Mainland China.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a tumor of the digestive tract with a high degree of malignancy, poor prognosis, and high mortality rate[1]. In recent years, the application of surgery combined with neoadjuvant chemotherapy has prolonged the survival of PDAC patients. However, PDAC patients undergoing chemotherapy experience surgical and chemotherapy-induced adverse events, negative emotions, changes in family and social relationships, and high treatment expenses; all of which can negatively influence health outcomes[2]. As an important part of human health, spiritual wellbeing emphasizes the role of maintaining optimistic and positive attitudes while self-regulating negative emotions when coping with stressful events. Studies have shown that spiritual wellbeing is positively correlated with health and contributes to better prognosis and quality of life[3,4]. Therefore, identifying the core factors influencing spiritual wellbeing of PDAC patients undergoing chemotherapy and formulating individualized spiritual care regimens can improve quality of life among this patient group. However, there have only been a few small studies of the spiritual wellbeing of PDAC patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear[5,6]. Therefore, this study was designed to identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy to provide a theoretical basis for formulating individualized spiritual care regimens.

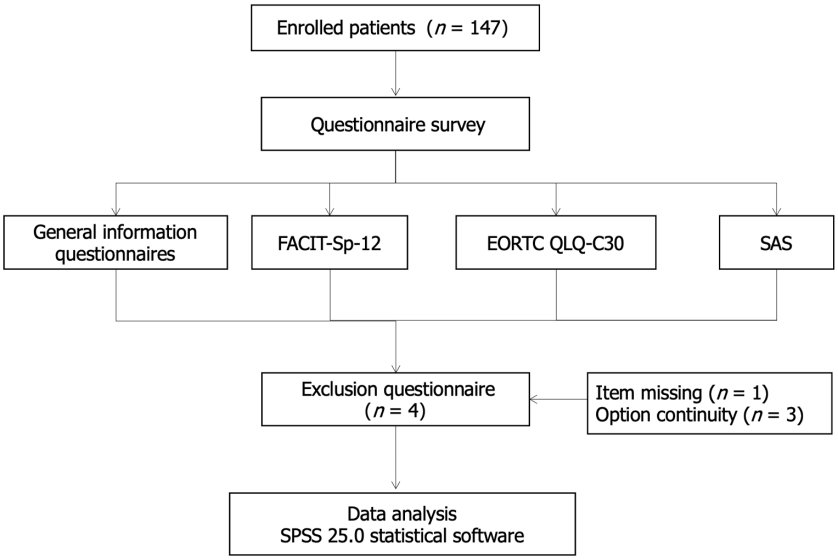
MATERIALS AND METHODS

Sample size calculation

According to the sample size estimation method in *Nursing Research Methods*[7], sample size should be 5–10 times the number of independent variables. Twenty-two independent variables were included in this study, and a nonresponse rate of 10% was considered as the upper limit. According to the formula, n = 22 × (5-10) × (1+10%), the sample size should range from 121 to 242.

Patient characteristics

PDAC patients receiving cyclic adjuvant chemotherapy in our department from January 2022 to December 2022 were recruited, and 147 questionnaires were distributed and collected with a recovery rate of 100%. After four invalid questionnaires were excluded, 143 were finally included in this study with an effective recovery rate of 97.28% (Figure 1). Inclusion criteria were: (1) Diagnosis of PDAC; (2) classified as locally progressive stage disease; (3) age 18–75 years; (4) requiring cyclic chemotherapy; and (5) clearly expressed willingness to participate in the study. Exclusion criteria were: (1) Mental illness or cognitive dysfunction; and (2) insufficient energy or physical strength to complete the questionnaire.



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Figure 1 Flowchart of the study design. FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale; SAS: Zung's Self-rating Anxiety Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Study tools

General information questionnaire: A self-designed questionnaire was distributed with items on gender, age, educational level, occupation, family income, marital status, religious beliefs, number of children, medical expenses, date of disease diagnosis, and recurrence of the disease.

Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale (FACIT-Sp-12): Spiritual well-being was measured by the FACIT-Sp-12 originally formulated by Brady *et al*[8] and translated into Mandarin by Liu *et al* [9]. Each item was scored on a 5-point Likert scale and assessed on three dimensions: faith, meaning, and peace, with higher scores indicating greater spiritual wellbeing. The Cronbach's α coefficient ranged from 0.711 to 0.920 with high validity, indicating that the FACIT-Sp-12 can be widely applied among cancer patients for the assessment of spiritual wellbeing.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30): The EORTC QLQ-C30 was a standard questionnaire designed for cancer patients by EORTC. It consisted of 30 items assessing eight quality of life dimensions. Items 29 and 30 were divided into seven levels, and scores ranged from 1 to 7 points, while all other items were scored on a 4-point Likert scale. For the functional and global health status domains, higher scores were indicative of better quality of life. For the symptom domain, a higher score indicated worse quality of life. The reliability of EORTC QLQ-C30 was 0.988 and validity was 0.989[10].

Zung's Self-rating Anxiety Scale (SAS): The SAS was designed by William W.K. Zung to reflect the degree of anxiety among patients. All items were graded on a 4-point Likert scale. A score < 50 was considered indicative of little or no anxiety, 50–60 of mild anxiety, 61–70 of moderate anxiety, and > 70 of severe anxiety[11].

Data collection methods

Prior to the survey, all investigators received standardized training to guarantee the objectivity and accuracy of data collection. All scales were completed by scanning QR codes. During the survey, investigators explained the response method and precautions for each scale by unified instructions. Each section of the questionnaire was completed by the patients independently or with the assistance of investigators. Investigators addressed any questions from patients to ensure the efficiency of questionnaire completion. After the survey, investigators examined whether any item was missing and instructed the patients to supply the missing response. Each scale required < 10 min to complete.

Statistical analysis

All data were analyzed using SPSS version 25.0 software. Quantitative data were expressed as frequency and percentage, and qualitative data as mean ± SD if it was under normal distribution. Total questionnaire scores and domain scores were compared among subgroups using the independent samples *t*-test or one-way analysis of variance (ANOVA) as indicated. Associations among total scores and domain were first assessed using Pearson's correlation analysis. Potential factors influencing spiritual wellbeing were then included in a multiple logistic regression model. A $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

RESULTS

Questionnaire results

The total score of FACIT-Sp-12 of PDAC patients treated with chemotherapy was (32.16 ± 10.06), (10.85 ± 3.76) for the dimension of faith, (10.55 ± 3.42) for meaning and (10.76 ± 4.00) for peace, respectively. The SAS score was calculated as (45.59 ± 6.44). The EORTC QLQ-C30 score was (83.74 ± 2.85), (74.01 ± 21.41) for global health status and (8.88 ± 1.79) for the symptom domain. The results of all questionnaires are summarized in Table 1.

Differences in spiritual wellbeing among demographic and clinical subgroups

Significant differences were observed in the spiritual wellbeing regarding sex, education level, household monthly income, type of health insurance and recurrence of PDAC patients treated with chemotherapy. Spiritual wellbeing scores were higher in males than females, in higher-educated compared to less-educated patients, and in patients at first diagnosis (without recurrence) (all $P < 0.05$), but showed no significant difference among age group, duration of illness, or occupational group (Table 2). Further, scores also differed by household monthly income and type of health insurance (both $P < 0.05$). The spiritual wellbeing score of patients with a household monthly income of 3000–5000 Yuan was the highest up to (35.00 ± 8.64), and the lowest score was (29.37 ± 10.65) in their counterparts with income of 1000–3000 Yuan. Patients with workers' medical insurance had the highest spiritual wellbeing score of 35.68 ± 7.80, and those with other types of health insurance obtained the lowest score of 19.42 ± 11.87.

Associations of spiritual wellbeing with anxiety and quality of life

The correlation coefficients between spiritual wellbeing and anxiety, and symptom domain of EORTC QLQ-C30 were calculated as -0.357 and -0.322, and those between spiritual wellbeing and global health status, and function domain were 0.464 and 0.421 ($P < 0.05$). These findings suggested that spiritual wellbeing was negatively correlated with anxiety level as measured by the SAS score and with the quality of life symptom domain according to EORTC QLQ-C30. The high spiritual wellbeing was predictive of lower anxiety and better symptom-related quality of life. Conversely, heightened anxiety and severity of symptoms were associated with lower spiritual wellbeing. In addition, spiritual wellbeing was positively correlated with global health status and the functional role domain of quality of life (all $P < 0.05$) (Table 3).

Independent factors predictive of spiritual wellbeing

In multivariate regression analysis, FACIT-Sp-12 total score was considered the dependent variable and all variables significantly associated with the wellbeing score in ANOVA (anxiety, functional role domain of EORTC QLQ-C30, global health status, and symptom domain) were included as independent variables (default values are shown in Table 4). Educational level, type of health insurance, functional role domain of the EORTC QLQ-C30, symptom domain of the EORTC QLQ-30, and global health status of the EORTC QLQ-30 were identified as independent factors influencing spiritual wellbeing (overall $R^2 = 0.502$, $P < 0.05$) (Table 5).

DISCUSSION

Spiritual wellbeing of PDAC patients treated with chemotherapy needs to be enhanced. The total spiritual wellbeing score for patients with PDAC undergoing chemotherapy was in the mid-range (32.16 ± 10.06), consistent with other patient populations described by Xue *et al*[12] and Liu *et al*[13], and indicating the need for improvement through spiritual care regimens. The diagnosis of PDAC places heavy emotional and financial burdens on patients[14]. Although surgery combined with neoadjuvant chemotherapy can prolong survival[15], the overall survival rate is still low[16], which increases uncertainty about life and reduces patient confidence in treatment outcome. Cyclic chemotherapy is a substantial imposition, disrupting lifestyle and social participation, with side effects including physical pain and other discomforts that further increase the psychological burden[13], which may eventually lower spiritual wellbeing. Therefore, medical staff should actively provide spiritual support, identify patients' negative emotions, strengthen health education, emphasize the importance of companionship, and create a positive atmosphere. Potential strategies included sharing treatment success stories, encouraging patients to reflect on the meaning of life, and alleviating negative emotion to help the patient achieve harmony of body, heart, and spirit.

Individual differences in spiritual wellbeing were related to demographics and clinical status. Although PDAC incidence was lower in females than males, the former reported significantly lower spiritual wellbeing, possibly due to a greater propensity for negative emotions in response to stressful events[17,18]. However, at present, the causes of gender difference on spiritual wellbeing are still unclear and warrant further investigation to formulate gender-specific spiritual care regimens for PDAC patients undergoing chemotherapy. Patients with higher educational level reported greater spiritual wellbeing. Many of these patients also reported a heavy economic burden (76%), which may explain why spiritual wellbeing was higher among PDAC patients in households with a monthly income of 3000–5000 Yuan compared to those with income of 1000–3000 Yuan. However, several studies[19-21] have found that household income was not an influencing factor on the spiritual wellbeing of cancer patients. Patients with higher household monthly incomes and urban medical insurance experience less pressure from medical expenses and were able to afford better chemotherapy; therefore, this group of patients could maintain a better quality of life. Nonetheless, the subgroup of patients with monthly income > 5000 Yuan did not have significant additional benefits, possibly due to the small sample size. Recurrence of PDAC was also an influencing factor for spiritual wellbeing as recurrence can intensify uncertainty and

Table 1 Questionnaire results for pancreatic ductal adenocarcinoma patients treated with chemotherapy (*n* = 143)

Item	Score range	Scale score	mean item score
FACIT-Sp-12	0-48	32.16 ± 10.06	2.68 ± 0.84
Faith	0-16	10.85 ± 3.76	2.71 ± 0.94
Meaning	0-16	10.55 ± 3.42	2.64 ± 0.86
Peace	0-16	10.76 ± 4.00	2.69 ± 1.00
SAS	0-100	45.59 ± 6.44	2.28 ± 0.32
Anxiety	0-20	5.48 ± 1.96	1.37 ± 0.49
Vegetative disorder	0-40	11.01 ± 2.90	1.38 ± 0.36
Exercise-induced anxiety	0-30	15.43 ± 2.40	2.57 ± 0.40
Concurrent symptoms of anxiety and vegetative disorder	0-10	4.54 ± 1.27	2.27 ± 0.64
EORTC QLQ-C30	0-100	83.74 ± 2.85	5.58 ± 0.19
Body	0-100	18.46 ± 15.52	3.69 ± 3.10
Role functioning	0-100	16.32 ± 19.33	8.16 ± 9.67
Emotion	0-100	14.74 ± 18.65	3.69 ± 4.67
Cognition	0-100	19.35 ± 19.74	9.67 ± 9.87
Social function	0-100	28.79 ± 24.80	14.39 ± 12.40
QLQ-C30 global health status	0-100	74.01 ± 21.41	37.00 ± 10.70
QLQ-C30 symptom domain	0-11	8.88 ± 1.79	0.68 ± 0.14
Fatigue	0-100	75.76 ± 21.04	25.25 ± 7.01
Nausea and vomiting	0-100	89.04 ± 17.48	44.52 ± 8.74
Pain	0-100	82.63 ± 21.29	41.32 ± 10.65
Shortness of breath	0-100	85.32 ± 21.89	
Insomnia	0-100	76.46 ± 27.07	
Loss of appetite	0-100	76.22 ± 27.59	
Constipation	0-100	86.71 ± 20.98	
Diarrhea	0-100	86.71 ± 20.98	
Economic difficulty	0-100	85.55 ± 25.50	

FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale; SAS: Zung's Self-rating Anxiety Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

reduce individual capacity to resolve difficulties, thereby lowering spiritual wellbeing. Medical staff should act to address issues such as economic pressure, negative emotions, and poor knowledge of treatment benefits and challenges, especially among female patients, to improve spiritual wellbeing.

In this study, the mean SAS score was in the very low range, albeit higher than reported previously[5] and was negatively correlated with spiritual wellbeing. Symptoms such as dyspnea (83.91%), irritation (78.32%), fatigue (51.05%), poor sleep (48.25%), and gastrointestinal reactions (46.15%) can induce anxiety. Long-term anxiety among these patients may evoke hypersensitivity to negative events, causing loss of faith in the treatment process, reducing optimism, and even leading to suicide[22,23]. Therefore, medical staff should closely monitor and attempt to mitigate anxiety by regulating respiratory and gastrointestinal functions, improving sleep and psychological state, encouraging patients to express their true emotions, mentally preparing patients to face negative events with a peaceful attitude, and strengthening their optimism.

High quality of life related to functional role and global health status can enhance spiritual wellbeing. In contrast, the functional role domain score and global health status score were predictive of greater spiritual wellbeing. More than 60% of these patient were unable to perform persistent physical activities due to advanced stage disease[24], which can interfere with family life and social activities, thereby provoking negative emotions. The difficulties in long cycles of treatment and the unpredictable health outcome may cause substantial anxiety, leading to negative emotions, reluctance to communicate with others, and ultimately loss of faith and meaning in life. Patients with high social support were more inclined to welcome alternative opinions and enjoy the companionship of others to relieve stress, find peace of mind, and

Table 2 Differences in spiritual wellbeing among demographic and clinical subgroups of pancreatic ductal adenocarcinoma patients on chemotherapy (*n* = 143)

Item		No. of cases, *n* (%)	Spiritual wellbeing score	*T*/*F*	*P* value
Sex	Male	93 (65.0)	32.89 ± 10.54	1.187	0.024
	Female	50 (35.0)	30.80 ± 9.06		
Age (yr)	18–44	18 (12.6)	29.67 ± 10.32	0.495[1]	0.687
	45–59	79 (55.2)	32.39 ± 10.16		
	60–74	36 (25.2)	32.39 ± 10.52		
	75–89	10 (7.0)	32.16 ± 10.06		
Education level	Primary school or below	37 (25.9)	26.03 ± 10.48	12.399[1]	< 0.001
	Middle and high school	62 (43.4)	32.19 ± 9.33		
	Technical and further education	20 (14.0)	33.6 ± 7.00		
	Undergraduate degree or above	24 (16.8)	40.33 ± 7.10		
Occupation	Farmer	73 (51.0)	32.49 ± 10.55	1.047[1]	0.374
	Retired	34 (23.8)	32.21 ± 10.23		
	Full-time employment	20 (14.0)	28.90 ± 9.99		
	Other	16 (11.2)	34.63 ± 6.86		
Household monthly income	> 1000 Yuan	35 (24.5)	31.03 ± 11.09	2.685[1]	0.049
	1000–3000 Yuan	30 (21.0)	29.37 ± 10.65		
	3000-5000 Yuan	56 (39.2)	35 ± 8.64		
	5000 Yuan plus	22 (15.4)	30.55 ± 9.80		
Spouse	Yes	124 (86.7)	31.59 ± 10.05	-1.749	0.082
	No	19 (13.3)	35.89 ± 9.57		
Religious belief	Yes	3 (2.1)	35 ± 14.73	0.493	0.623
	No	140 (97.9)	32.1 ± 10.01		
Number of offspring	0	4 (2.8)	39 ± 4.24	1.654[1]	0.180
	1	65 (45.5)	33.42 ± 9.37		
	2	58 (40.6)	31.10 ± 10.37		
	3 or more	16 (11.2)	29.19 ± 11.77		
Type of health insurance	Employee Health Insurance	62 (43.4)	35.68 ± 7.80	11.282[1]	< 0.001
	New rural pension scheme	63 (44.1)	30.98 ± 9.65		
	Urban medical insurance	6 (4.2)	33.67 ± 10.35		
	Other	12 (8.4)	19.42 ± 11.87		
Time after diagnosis	≤ 6 mo	69 (48.3)	33.42 ± 8.44	1.278[1]	0.284
	7–12 mo	40 (28.0)	30.95 ± 11.11		
	13–24 months	17 (11.9)	28.76 ± 13.26		
	≥ 24 mo	17 (11.9)	33.29 ± 9.76		
Recurrence	Yes	28 (19.6)	26.18 ± 12.19	-3.035	< 0.001
	No	115 (80.4)	32.16 ± 10.06		

[1]*F* test.

Table 3 Correlations among spiritual wellbeing, anxiety, and quality of life scores (*n* = 143)

Item	Spiritual wellbeing	Faith	Meaning	Peace
SAS	-0.357[b]	-0.329[b]	-0.345[b]	-0.293[b]
Anxiety	-0.371[b]	-0.366[b]	-0.319[b]	-0.316[b]
Vegetative disorder	-0.466[b]	-0.420[b]	-0.469[b]	-0.378[b]
Exercise-induced anxiety	0.053	0.067	0.047	0.030
Concurrent symptoms of anxiety and vegetative disorder	0.092	0.061	0.079	0.106
EORTC QLQ-C30	0.421[b]	0.381[b]	0.437[b]	0.329[b]
Body	0.292[b]	0.302[b]	0.266[b]	0.225[b]
Role functioning	0.181[a]	0.177[a]	0.223[b]	0.100
Emotion	0.436[b]	0.387[b]	0.436[b]	0.362[b]
Cognition	0.324[b]	0.275[b]	0.335[b]	0.271[b]
Social function	0.301[b]	0.229[b]	0.368[b]	0.229[b]
QLQ-C30 global health status	0.464[b]	0.362[b]	0.435[b]	0.456[b]
QLQ-C30 symptom domain	-0.322[b]	-0.320[b]	-0.331[b]	-0.226[b]
Fatigue	-0.264[b]	-0.294[b]	-0.245[b]	-0.177[a]
Nausea and vomiting	-0.169[a]	-0.210[a]	-0.144	-0.105
Pain	-0.275[b]	-0.278[b]	-0.294[b]	-0.180[a]
Shortness of breath	-0.214[a]	-0.231[b]	-0.183[a]	-0.166[a]
Insomnia	-0.281[b]	-0.229[b]	-0.302[b]	-0.234[b]
Loss of appetite	-0.309[b]	-0.295[b]	-0.323[b]	-0.225[b]
Constipation	-0.189[a]	-0.213[a]	-0.183[a]	-0.119
Diarrhea	-0.199[a]	-0.162	-0.242[b]	-0.143
Economic difficulty	-0.098	-0.042	-0.156	-0.074

[a]$P < 0.05$.
[b]$P < 0.01$. SAS: Zung's Self-rating Anxiety Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Table 4 Default values of independent variables for multivariable regression

Independent variable	Default value
Sex	Male = 1; female = 2
Education level	Primary school or below = 1; middle and high school = 2; technical and further education = 3; bachelor degree and above = 4
Household monthly income (Yuan)	< 1000 = 1; 1000-3000 = 2; 3000-5000 = 3; > 5000 = 4
Type of health insurance	Workers' medical insurance = 1; new rural pension scheme = 2; urban medical insurance = 3; other = 4
Recurrence	Yes = 1; No = 2

better adapt to life challenges. Therefore, medical staff should provide comprehensive and individualized spiritual care aiming to assist and encourage patients to positively accept and face negative events through disease cognition, psychological counseling, and life review.

The symptom domain of quality of life negatively affects spiritual wellbeing, suggesting that severe symptoms and concomitant poor quality of life can degrade spiritual wellbeing. This was consistent with the findings of Du *et al*[25], who also found that most PDAC patients treated with chemotherapy developed symptoms such as fatigue (68%) and insomnia (52%), which may have persisted during the course of treatment[26]. Patients with chronic fatigue were prone to express negative emotions, while discomfort from cyclic chemotherapy and chronic disease pain aggravated insomnia and lowered life expectations[27,28]. Consequently, medical staff should closely monitor adverse symptoms such as

Table 5 Multiple linear regression analysis of factors independently influencing spiritual wellbeing (*n* = 143)

Item	FACIT-Sp-12				
	b	sb	b'	*t* value	*P* value
(Constant)	-74.696	42.693	-	-1.750	0.082
Sex	0.518	1.397	0.025	0.371	0.711
Education level	3.297	0.639	0.332	5.156	< 0.001
Household monthly income	0.013	0.65	0.001	0.020	0.984
Type of health insurance	-3.02	0.798	-0.263	-3.786	< 0.001
recurrence	2.198	1.739	0.087	1.264	0.209
SAS anxiety	-0.214	0.12	-0.137	-1.786	0.076
C30 global health status	0.988	0.416	0.279	2.371	0.019
C30 symptom domain	0.152	0.037	0.323	4.117	< 0.001
C30 functional domain	1.647	0.643	0.293	2.559	0.012

F = 14.902, P = 0.000, R = 0.709, R^2 = 0.502. FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale.

fatigue and insomnia to alleviate discomfort and improve life expectations, possibly *via* family guidance and mindfulness meditation.

This study had several limitations. Most patients were from southwestern China (Chongqing) and so this may not be a nationally representative sample. Future studies will expand the sample size and evaluate the effects of specific religious beliefs on the spiritual wellbeing of PDAC patients receiving chemotherapy.

CONCLUSION

Education level, health insurance category, symptom domain, functional role domain and global health status were the main factors influencing spiritual wellbeing among PDAC patients undergoing chemotherapy. Individualized spiritual care regimens can be formulated through life care, behavioral therapy, mindfulness meditation, cognitive interview, and life review among other strategies.

ARTICLE HIGHLIGHTS

Research background

Identifying the core factors influencing spiritual wellbeing of pancreatic ductal adenocarcinoma (PDAC) patients undergoing chemotherapy and formulating individualized spiritual care regimens can improve quality of life among this patient group. However, there have only been a few small studies of the spiritual wellbeing of PDAC patients undergoing chemotherapy. The core factors influencing spiritual wellbeing in this clinical population are still unclear. Therefore, this study was designed to identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy.

Research motivation

This study was designed to investigated the spiritual wellbeing status and identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy. To draw attention to the spiritual health of patients with pancreatic cancer undergoing chemotherapy and formulate individualized spiritual care regimens.

Research objectives

This study was designed to investigated the spiritual wellbeing status and identify factors influencing the spiritual wellbeing of PDAC patients undergoing chemotherapy. This study found that effective measures to mitigate anxiety and increase quality-of-life-related role functioning, emotional guidance, cognition of disease, social function, and life education may enhance spiritual wellbeing. Individualized spiritual care regimens can be formulated through life care, behavioral therapy, mindfulness meditation, cognitive interview, and life review among other strategies.

Research methods

The research method of this study was a questionnaire survey. Prior to the questionnaire survey, all investigators received standardized training to guarantee the objectivity and accuracy of data collection. The questionnaire included a

general information questionnaire, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being 12 Item Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Zung's Self-rating Anxiety Scale. All data were analyzed using SPSS version 25.0. $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

Research results

This study investigated the spiritual wellbeing of Chinese patients with PDAC undergoing chemotherapy and analyzed its influencing factors for the first time. This study found that individualized spiritual care regimens can be formulated through life care, behavioral therapy, mindfulness meditation, cognitive interview, and life review among other strategies. This study had limitations. Most patients were from southwestern China (Chongqing), so this may not be a nationally representative sample. Future studies will expand the sample size and evaluate the effects of specific religious beliefs on the spiritual wellbeing of PDAC patients receiving chemotherapy.

Research conclusions

Spiritual wellbeing of PDAC patients treated with chemotherapy was in the mid-range, and individual differences in spiritual wellbeing related to demographics and clinical status. Anxiety and symptom severity markedly disrupted the spiritual wellbeing of PDAC patients undergoing chemotherapy, whereas a sustained functional role and good global health status related to quality of life promoted spiritual wellbeing. This study provides a theoretical basis for formulating individualized spiritual care regimens.

Research perspectives

Future studies will expand the sample size and evaluate the effects of specific religious beliefs on the spiritual wellbeing of PDAC patients receiving chemotherapy.

FOOTNOTES

Author contributions: Wei LL, Zhang ST contributed to the conception and design of the study; Wei LL and Zhang ST contributed equally to this work as joint first authors; Mi N contributed to the administrative support; Liao Y contributed to the provision of study materials or patients; Zhang ST, Liao Y, Zhang Y, Yu Y collected and analyzed the data; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Organized physical activity and sedentary behaviors in children and adolescents with autism spectrum disorder, cerebral palsy, and intellectual disability

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Abstract

BACKGROUND

There is little data on physical activity (PA), organized PA (OPA), and sedentary behaviors in autism spectrum disorders (ASD) and other neurodevelopmental disorders in developing countries.

AIM

To examine OPA, non-OPA, and sedentary behaviors and their associated factors in children and adolescents with ASD, cerebral palsy (CP), and intellectual disability (ID).

METHODS

A total of 1020 children and adolescents with ASD, CP, and ID were assessed regarding the child and family information as well as the Children's Leisure Activities Study Survey.

RESULTS

The results showed that the OPA level was significantly lower than non-OPA in all groups. Furthermore, the OPA level was significantly lower in the CP group compared to ASD and ID groups ($P < 0.001$). Also, moderate ($P < 0.001$), vigorous ($P < 0.05$), and total ($P < 0.001$) physical activity levels were significantly different between all three groups, with the values being higher in the ASD group

compared to the other two. The mean of the total sedentary behavior duration in the ASD group (1819.4 min/week, SD: 1680) was significantly lower than in the CP group (2687 min/week, SD: 2673) (P = 0.007) but not ID group (2176 min/week, SD: 2168.9) (P = 0.525).

CONCLUSION

Our findings remark on the participation rate of PA, OPA, and sedentary behaviors of children and adolescents with ASD, CP, and ID in a developing country. In contrast, the need for developing standards of PA/OPA participation in neurodevelopmental disorders is discussed.

Key Words: Neurodevelopmental disorders; Physical disability; Mental disability; Active lifestyle

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Core Tip: There is little data on physical activity (PA), organized PA (OPA), and sedentary behaviors in autism spectrum disorder (ASD) and in developing countries. A total of 1020 children and adolescents with ASD, cerebral palsy (CP), and intellectual disability (ID) were assessed regarding their physical activity. Our findings remark on the participation rate of PA, OPA, and sedentary behaviors of children and adolescents with ASD, CP, and ID in a developing country.

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INTRODUCTION

Sedentary behavior has been defined as any waking behavior with an energy expenditure ≤ 1.5 metabolic equivalents while in a sitting, reclining, or lying posture and is associated with chronic underlying diseases such as diabetes and cardiovascular diseases[1-3]. On the other hand, non-organized physical activity (PA) is defined as any bodily movement that requires energy expenditure higher than sedentary behavior level, and organized PA (OPA) is defined as involving in regular and structured health and leisure activities with peers, coaches, and group leaders such as tennis, football, etc [4].

Plenty of literature points to the importance of PA in children; however, levels of PA are insufficient for different groups of children, particularly those with disabilities[5]. The optimal level of PA can increase health status and decrease the incidence of chronic disorders such as cancer, diabetes, cardiovascular disorders, and mood disorders[6]. Mental, intellectual, and motor disabilities negatively impact the opportunities to participate in an optimal level of PA to gain health benefits and limit sedentary behaviors consequences[7]. In other words, children with particular disabilities, such as neurodevelopmental disorders, may be limited regarding motor disabilities and social skills[8]. For example, children with autism spectrum disorders (ASD) participate in less PA[9] and more sedentary behaviors than their peers leading to greater body mass index (BMI) in comparison to typically developing (TD) children[10-12]. In addition, according to estimates of developed countries, children with neurodevelopmental disorders such as ASD, cerebral palsy (CP), and intellectual disability (ID) also participated less in a regular and OPA than those children without a neurodevelopment disability[13-17]. Studies have also shown children with neurodevelopmental disabilities encounter additional personal and environmental barriers that hinder their participation in physical activities compared to TD children[10,18].

Although the disability characteristics should be considered[8], participation in PA, benefiting from its psychosocial and motor advantages, is of paramount importance for children with neurodevelopmental disorders[8,19]. PA could also enhance cognitive and meta-cognitive function and improve educational performance[20-22]. Moreover, OPA provides additional benefits, including promoting inclusion, facilitating social connection, improving social and emotional well-being, and reducing functional decline[23]. For example, Sun *et al*[24], in a clinical trial, assessed the effects of an adapted PA consisting of moderate-intensity aerobic and resistance exercises on health-related physical fitness in adolescents with ID. The authors declared significant changes were observed in cardiorespiratory fitness, running/walking tests, and flexibility in the intervention group compared to the control group. In addition, in a recent systematic review and meta-analysis, Howells *et al*[23] represented that group-based OPA participation improves overall social functioning in children with ASD. Moreover, Mak *et al*[25] reported the positive effect of a regular 8-wk mindfulness yoga program on attention outcomes of children with CP. However, due to motor skill limitations, such a positive impact was not observed in their physical skills outcomes. Given the above, OPA is a constructive and helpful context in which children and adolescents with neurodevelopmental disorders could benefit from opportunities, including social engagement, promoting social skills, enhancing mental health, and improving quality of life[26,27].

Despite valuable research in terms of the effect of PA and OPA on different aspects of neurodevelopmental disorders, there are few studies assessing the rate of OPA participation in children with ASD in comparison to other neurodevelop-

mental groups and not TD children. Arim *et al*[8] assessed the PA/OPA participation rate in 4-9 years old Canadian children with neurodevelopmental disorders (including epilepsy, CP, ID, and learning disability) compared to TD children. Their results represented that although the frequency of OPA participation in this population varied depending on the child's health condition, there was no significant difference in general PA participation among different neurodevelopmental groups.

Thus, the current study aimed to assess and compare sedentary behavior, OPA, and non-OPA levels, as primary outcomes in children and adolescents with ASD, ID, and CP. We also aimed to determine the personal and familial factors associated with PA and sedentary behavior among these children. This is one of the few studies on PA levels among children with neurodevelopmental disorders in the context of a developing country, utilizing a large sample size. The findings of this study may help to identify the groups which benefit the most from the interventions to improve PA levels and can be a basis for future studies in the context of developing countries.

MATERIALS AND METHODS

Study design and setting

The data for the current cross-sectional study were drawn from a longitudinal survey of "Quality of life and psycho-physical function in children and adolescents with developmental disabilities; evaluating risk factors and developmental trend", which was conducted from 2011 to 2021 with a sample size of 1850 participants (1040 boys and 810 girls) aged 6-18 years from special schools in Tehran, Iran. Participants were included in the study by stratified random sampling. The population was stratified into different strata by disorders; each stratum was divided into different clusters (schools), respectively. Then five schools were included for each stratum (disorder). Afterward, children's parents/caregivers responded to the Children's Leisure Activities Study Survey (CLASS questionnaire) to examine the children's non-OPA (*i.e.*, general routine PA), OPA, and sedentary behavior activities. The study was approved by the ethics committee of Tehran University of medical sciences (ethics code: IR.TUMS.NI.REC.1401.031), and written consent was obtained from participants' parents/caregivers before entering the study.

Participants

Children and adolescents with neurodevelopmental disorders were included in the current study. The diagnosis of ASD was confirmed by DSM-IV, and the autism diagnostic inventory-revised by a professional child psychiatrist. The participants were excluded if they had two or three of the conditions (*i.e.*, ASD, CP, or ID) together and being less than six years of age.

Measurements

Basic and sociodemographic data: Parents/caregivers of the participants were asked to fill the items of a questionnaire containing child and family basic and sociodemographic information, including the child's age, gender, childcare status (two parents, single parent, and other), household status (owner, tenant, and other), parents' age, and parents' educational level. Physical therapists also conducted a physical examination to measure participants' height, weight, waist circumference, and hip circumference. Moreover, the existence of any musculoskeletal disorder preventing physical movements was assessed based on physical examination as well as the participants' medical history by a physical therapist.

Non-OPA/OPA and sedentary behavior data: We used the Persian version of the CLASS to assess non-OPA/OPA and sedentary behavior. This survey measures the type, frequency, and duration of different types of PA, including non-OPA and OPA as well as sedentary behavior among children. The CLASS checklist contains items for both non-OPA (such as playing indoors with toys, walking the dog, *etc.*) and OPA (such as football, basketball, aerobics, *etc.*), as well as items for sedentary behaviors (such as sitting, talking, listening to music, and reading). Previous studies have demonstrated test-retest reliability (ICC > 0.58 across different domains) and criterion validity CLASS[28].

Statistical methods

First, descriptive statistics for basic, demographic, and sociodemographic variables, PA/OPA, and sedentary behavior data were calculated for each group. We used the chi-square test to compare the categorical variables between groups. We also used the Kolmogorov-Smirnov test to test if the continuous variables are distributed normally. As none of the continuous variables had normal distribution, we used non-parametric tests, such as the Kruskal-Wallis test, to compare them between groups. Moreover, the Mann-Whitney *U* test was also conducted to compare two individual groups whenever the difference between the three groups was significant. Finally, the Wilcoxon test was used to compare OPA and non-OPA levels in all groups. All analyses were conducted using SPSS version 26, while a *P* value of less than 0.05 was considered significant.

RESULTS

Descriptive statistics

In the current study, 1020 participants (ASD: 248, CP: 306, ID: 466) were included in the final analysis (Table 1 shows the

Table 1 Basic and demographic data of participants in autism spectrum disorders, intellectual disability, and cerebral palsy groups, *n* (%)

Variables	ASD	ID	CP	*P* value
Gender; Female	9 (3.6)	247 (53.0)	160 (52.3)	**< 0.001**
Age (yr); mean (SD)	11.15 (2.7)	12.69 (3.0)	12.11 (3.2)	**< 0.001**
Height (cm); mean (SD)	145.51 (16.20)	141.55 (17.30)	137.01 (18.70)	**< 0.001**
Weight (kg); mean (SD)	44.98 (19.10)	42.70 (18.10)	38.73 (20.70)	**< 0.001**
WC (cm); mean (SD)	70.90 (13.60)	72.19 (15.10)	66.53 (11.80)	**< 0.001**
HC (cm); mean (SD)	81.16 (12.60)	82.72 (15.40)	76.23 (12.80)	**< 0.001**
WHR; mean (SD)	0.86 (0.10)	0.87 (0.20)	0.87 (0.10)	0.691
Musculoskeletal disorder	27 (10.9)	70 (15.0)	78 (25.5)	**< 0.001**
Household				
Owner	131 (55.0)	239 (54.2)	108 (37.9)	**< 0.001**
Tenant	92 (38.7)	178 (40.4)	141 (49.5)	
Other	15 (6.3)	24 (5.4)	36 (12.6)	
Childcare				
Two parents	201 (91.8)	350 (85.8)	242 (89.3)	0.157
Single parent	17 (7.8)	48 (11.8)	25 (9.2)	
Other	1 (0.5)	10 (2.5)	4 (1.5)	
Father's education				
Lower than diploma	39 (16.5)	217 (48.5)	122 (43.9)	**< 0.001**
Diploma (11 yr of education)	70 (29.5)	134 (30.0)	89 (32.0)	
Higher than diploma	128 (54.0)	96 (21.5)	67 (24.1)	
Mother's education				
Lower than diploma	37 (15.3)	215 (48.4)	105 (36.1)	**< 0.001**
Diploma (11 yr of education)	85 (35.1)	159 (35.8)	132 (45.4)	
Higher than diploma	120 (49.6)	70 (15.8)	54 (18.6)	
Father's age (yr); mean (SD)	43.98 (6.70)	46.2 (7.7)	43.2 (6.9)	**< 0.001**
Mother's age (yr); mean (SD)	38.30 (6.50)	41.2 (7.1)	38.1 (6.7)	**< 0.001**

ASD: Autism spectrum disorders; CP: Cerebral palsy; HC: Hip circumference; ID: Intellectual disability; SD: Standard deviation; WC: Waist circumference; WHR: Waist to hip ratio.

descriptive statistics). In the ASD group, 3.6% of participants were female, which is significantly lower than the ID and CP groups (53% and 52.3%, respectively; $P < 0.001$). In pairwise comparison, there were significant differences between groups regarding their ages ($P < 0.05$), with the ASD group being the youngest (mean = 11.15, SD = 2.66) and the ID group being the oldest (mean = 12.69, SD = 3.15). Similarly, height was significantly different between all three groups ($P < 0.05$). Also, children with CP had lower weights ($P < 0.01$), smaller waist circumferences ($P < 0.01$), and smaller hip circumferences ($P \leq 0.001$) than the other groups. In addition, the prevalence of musculoskeletal disorders was significantly higher in the CP group compared to both ASD and ID groups ($P < 0.001$). The parents in the ASD group were more educated than both CP and ID groups ($P < 0.001$). Parents of children with ID were significantly older than the parents of the other two groups ($P \leq 0.001$).

Non-OPA/OPA and sedentary behavior results

Table 2 presents and compares the physical activity levels of children with ASD, ID, and CP. Our results showed that the level of OPA is significantly lower in comparison to non-OPA in ASD ($P < 0.001$), CP ($P < 0.001$), and ID ($P < 0.001$) groups (Table 2). Furthermore, the OPA level was significantly lower in the CP group compared to ASD and ID groups ($P < 0.001$). Also, non-OPA levels were significantly different between the three groups ($P < 0.001$). Also, in pairwise comparisons, moderate ($P < 0.001$), vigorous ($P < 0.05$), and total ($P < 0.001$) physical activity levels were significantly different between all three groups, with the values being higher in the ASD group compared to the other two.

Table 2 The amount of physical activity/organized physical activity (minutes per week) and level of physical activity in autism spectrum disorders in comparison to control intellectual disability, and cerebral palsy groups

Min/week	ASD, mean (SD)	ID, mean (SD)	CP, mean (SD)	*P* value
OPA				
Aerobic exercise	1.0 (8.7)	1.1 (10.2)	0.6 (6.5)	0.938
Dancing	7.3 (30.7)	14.2 (44.6)	6.9 (38.3)	**< 0.001**
Gymnastic	2.2 (24)	0.6 (8.1)	0.2 (3.1)	0.367
Tennis	0.4 (3.9)	2.0 (16.9)	4.7 (51.5)	0.323
Football	10.5 (59.4)	9.2 (34.4)	3.7 (28.2)	**0.003**
Volleyball	2.6 (29.2)	1.3 (9.4)	0.4 (4.3)	0.246
Basketball	0.8 (12.1)	2.3 (26.7)	0.3 (4.2)	0.475
Handball	0 (0)	0.1 (2.5)	0.3 (3.3)	0.132
Swimming laps	11.1 (58.2)	2.6 (17.4)	1.2 (10.2)	**0.008**
Rollerblading	4.2 (24.7)	3.6 (37.7)	0.2 (2.9)	**0.017**
Skateboarding	0.7 (8.3)	0.9 (15.4)	0.3 (4.2)	0.690
Physical education class	2.3 (14.7)	1.9 (11.5)	1.1 (8.6)	0.567
Sport class at school	16.4 (25.1)	10.5 (24.9)	6.6 (17.1)	**< 0.001**
Total OPA	59.5 (134.0)	50.4 (101.3)	26.6 (85.1)	**< 0.001**
Non-OPA (mins/week)				
Bicycling	27.4 (95.7)	11.7 (49.8)	9.4 (76.6)	**< 0.001**
Scooter	6.9 (37)	4.0 (29.3)	0.5 (4.6)	**0.008**
Skipping rope	1.6 (17.2)	0.8 (5.8)	0.3 (3.6)	**0.047**
Playing with the ball	0.7 (7.9)	1.7 (29.4)	0.3 (5.1)	0.377
Tag/chasey	2.1 (20.8)	3.8 (20.8)	0.6 (7.3)	**< 0.001**
Household chores	23.5 (70.7)	26.3 (94.8)	10.6 (53)	**< 0.001**
Walk for exercise	49.7 (103.5)	23.7 (55.9)	22.7 (135.6)	**< 0.001**
Play on playground equipment	48.2 (95.7)	22.7 (53.9)	13.6 (43.5)	**< 0.001**
Jogging or running	17.4 (82.6)	9.2 (35.0)	4.1 (22.1)	**< 0.001**
Swimming for fun	21.8 (48.6)	6.6 (25.1)	9.8 (34.5)	**< 0.001**
Bounce on the trampoline	4.9 (30.1)	1.5 (15.3)	0.5 (4.9)	**< 0.001**
Play with pet	2.3 (18.6)	3.7 (24)	5.5 (41.9)	0.471
Travel to school by walking	4.0 (21.3)	6.1 (31.9)	1.2 (9.8)	**< 0.001**
Travel to school by bicycling	0.2 (3.8)	0.2 (2.4)	0.1 (2.3)	0.822
Total non-OPA	210.8 (295.3)	122.1 (210.1)	79.4 (207.5)	**< 0.001**
Level of PA/OPA				
Moderate physical activity	198.7 (277.1)	129.4 (206.9)	79.8 (207.2)	< 0.001
Vigorous physical activity	71.5 (159.4)	43.1 (111.9)	26.1 (84.2)	< 0.001
Total physical activity	270.3 (372.9)	172.4 (275.3)	105.9 (241.8)	< 0.001

PA: Physical activity; OPA: Organized physical activity; ASD: Autism spectrum disorders; CP: Cerebral palsy; ID: Intellectual disability; SD: Standard deviation.

Table 3 The amount of sedentary behavior (minutes per week) in autism spectrum disorders in comparison to control intellectual disability, and cerebral palsy groups

Variables (mins/week)	ASD, mean (SD)	ID, mean (SD)	CP, mean (SD)	*P* value
Watching TV	465.8 (628.1)	709.8 (810.0)	747.3 (788.9)	**< 0.001**
Play station/computer games	131.7 (306.9)	96.2 (281.8)	103.1 (309.4)	0.061
Computer/internet	74.9 (215.7)	70.5 (229.9)	69.0 (270.1)	0.185
Homework	363.1 (410.6)	415.2 (489.0)	516.6 (717.0)	0.392
Play indoors with toys	136.7 (277.4)	164.1 (315.4)	193.7 (359.0)	0.742
Sitting talking	112.7 (296.5)	170.3 (400.2)	293 (757.4)	0.052
Talk on the phone	16.8 (60.0)	38.2 (175.5)	67.1 (231.9)	**0.001**
Listen to music	177.4 (402.3)	121.9 (258.1)	118.3 (253.2)	0.118
Playing musical instrument	7.6 (37.4)	5.1 (62.3)	2.9 (27.9)	**0.005**
Playing board games/cards	15.7 (88.0)	15.9 (75.9)	27.4 (129.3)	0.249
Reading	98.1 (222.4)	146.6 (294.2)	250.2 (420.4)	**0.001**
Art	40.2 (128.3)	44.7 (169.5)	49.1 (234.6)	0.187
Imaginary play	24.0 (115.5)	72.3 (197.2)	89.1 (279.9)	**0.001**
Travel by car/bus	154.7 (357.6)	105.7 (296.1)	160.3 (372.4)	**0.032**
Total sedentary behavior	1819.4 (1680.0)	2176.5 (2168.9)	2687.0 (2673.5)	0.008

ASD: Autism spectrum disorders; CP: Cerebral palsy; ID: Intellectual disability; SD: Standard deviation.

Table 3 represents the sedentary behaviors of participants. The mean of the total sedentary behavior duration in the ASD group (1819.4 mins/week, SD: 1680) was significantly lower than in the CP group (2687 mins/week, SD: 2673; P = 0.007) but not ID group (2176 mins/week, SD: 2168.9; P = 0.525). There was also no significant difference between children with CP and ID concerning the time spent on sedentary behavior (P = 0.106).

Sociodemographic contributing factors

Tables 4-6 show the details of contributing factors for moderate to vigorous physical activities (MVPA) and sedentary behaviors in the ASD, ID, and CP groups, respectively. OPA was significantly lower in females (mean = 5.6, SD = 11.1) than males (mean = 61.6, SD = 136) in children with ASD (P = 0.045). Also, in the ASD group, non-OPA (P = 0.032) and sedentary behavior (P = 0.02) levels were significantly different in children of mothers with various educational levels (Table 4). Males in the ID group had higher MVPA (P < 0.001), OPA (P < 0.001), and non-OPA (P = 0.001) levels than the females. Household status (P = 0.018) and age (P = 0.004) were associated with OPA, while the presence of musculoskeletal disorders (P = 0.041) and household status (P = 0.008) were associated with sedentary behavior in the ID group (Table 5). Additionally, in this group, childcare status was associated with MVPA (P = 0.021) and non-OPA (P = 0.023). Gender was associated with MVPA (P = 0.091), OPA (P = 0.045), and sedentary behavior (P = 0.002) in children with CP. Also, household status (P = 0.018) and father's education (P = 0.029) were associated with sedentary behavior and OPA, respectively (Table 6).

DISCUSSION

Regular OPA and general PA help enhance psychosocial and health outcomes[29]. On the other hand, sedentary behaviors can indirectly increase the risk of various health conditions. It is worth noting that children and adolescents with disabilities have a lower participation rate in PA, putting them at higher risk for complications[30], which can cause significant challenges for the child, their families, and society[30]. Thus, we aimed to examine the participation rate of OPA, PA, and sedentary behaviors among children with neurodevelopmental disorders in a new sample from a developing country.

Interestingly, our findings showed that the amount of OPA is lower than non-OPA in all ASD, CP, and ID groups. Despite the known positive effects of group-based OPA in overall social functioning in children[23], it seems that the parents/caregivers of children with neurodevelopmental disorders still do not take advantage of regular OPA as a non-medical treatment for their children. Papadopoulos *et al*[31] examined parent-reported barriers to OPA, reported a lack of children's happiness and motivation during OPA as the main existing barriers to OPA among individuals with neurodevelopmental disorders. However, it seems that other hypothetical major barriers, such as the lack of appropriately adapted OPA programs and parents' unawareness of OPA's benefits, are also playing a role in developing

Table 4 Associations between contributing factors, moderate to vigorous physical activities,and sedentary behaviors in autism spectrum disorders group

Domain	Variable		MVPA (mins/week)	*P* value	OPA (mins/week)	*P* value	Non-OPA (mins/week)	*P* value	SB (mins/week)	*P* value
Individual	Gender	Male (*n* = 239)	276.7 (377.9)	0.127	61.6 (136.0)	**0.045**	215.1 (299.3)	0.310	1835.6 (1686.0)	0.418
		Female (*n* = 9)	100.6 (105.8)		5.6 (11.1)		95.0 (105.2)		1388.7 (1536.3)	
	Age	6-11 yr (*n* = 143)	308.1 (423.1)	0.381	64.3 (148.7)	0.484	243.8 (345.4)	0.313	1897.70 (1738.69)	0.733
		12-14 yr (*n* = 72)	200.1 (237.5)		48.5 (81.0)		151.5 (193.4)		1728.3 (1538.7)	
		15-18 yr (*n* = 33)	259.7 (319.3)		62.9 (159.4)		196.8 (218.6)		1679.1 (1747.5)	
	Musculoske-letal disorder	No (*n* = 221)	264.4 (380.2)	0.094	57.7 (136.1)	0.054	206.7 (301.6)	0.140	1774.4 (1666.3)	0.242
		Yes (*n* = 27)	318.9 (307.8)		74.6 (115.9)		244.2 (239.1)		2187.7 (1778.6)	
Familial/social	Household	Owner (*n* = 131)	252.2 (362.2)	0.897	59.1 (142.0)	0.880	193.1 (262.6)	0.985	1803.0 (1625.8)	0.986
		Tenant (*n* = 92)	288.3 (397.6)		65.7 (137.0)		222.7 (324.9)		1832.8 (1801.9)	
		Other (*n* = 15)	234.4 (223.1)		52.0 (74.8)		182.4 (206.6)		1846.0 (1729.3)	
	Child care	Two parents (*n* = 207)	285.5 (389.1)	0.258	63.8 (144.5)	0.624	221.8 (304.0)	0.325	1906.3 (1698.4)	0.493
		Single parent (*n* = 17)	202.9 (296.8)		29.4 (35.6)		173.5 (297.9)		1415.0 (1399.3)	
		Other (*n* = 1)	-		-		-		-	
	Father's education	Lower than diploma (*n* = 39)	309.3 (426.0)	0.335	58.5 (144.6)	0.060	250.8 (367.3)	0.672	1782.3 (1637.1)	0.099
		Diploma (*n* = 70)	264.2 (439.7)		62.4 (189.2)		201.8 (295.2)		1526.7 (1584.9)	
		Higher than diploma (*n* = 128)	269.0 (324.6)		60.7 (93.9)		208.3 (277.0)		2012.8 (1637.1)	
	Mother's education	Lower than diploma (*n* = 37)	229.9 (352.3)	0.076	37.8 (75.8)	0.443	192.0 (342.8)	**0.032**	1218.8 (1694.3)	**0.020**
		Diploma (*n* = 85)	323.1 (433.6)		70.0 (177.3)		253.1 (306.6)		1696.5 (1708.2)	
		Higher than diploma (*n* = 120)	251.5 (337.2)		59.9 (113.4)		191.6 (275.1)		1898.4 (1607.9)	
	Father's age	< 35 yr (*n* = 13)	204.2 (222.6)	0.484	36.9 (46.1)	0.496	167.3 (217.1)	0.538	1656.0 (2499.9)	0.223
		35-49 yr (*n* = 182)	297.0 (403.1)		64.7 (144.8)		232.3 (320.8)		1912.5 (1690.2)	
		≥ 50 yr (*n* = 40)	202.6 (244.1)		44.5 (93.9)		158.1 (190.8)		1472.0 (1329.6)	
	Mother's age	< 35 yr (*n* = 81)	327 (456.6)	0.168	71.7 (181.7)	0.544	255.4 (334.3)	0.228	1822.7 (1935.8)	0.218
		35-49 yr (*n* = 149)	258.2 (334.1)		56.3 (107.4)		202.0 (283.3)		1866.2 (1545.9)	
		≥ 50 yr (*n* = 13)	132.7 (177.1)		27.3 (53.4)		105.4 (132.2)		1123.5 (1129.0)	

OPA: Organized physical activity; SB: Sedentary behaviors MVPA: Moderate to vigorous physical activities

Table 5 Associations between contributing factors, moderate to vigorous physical activities,and sedentary behaviors in intellectual disability group

Domain	Variable		MVPA (mins/week)	*P* value	OPA (mins/week)	*P* value	Non-OPA (mins/week)	*P* value	SB (mins/week)	*P* value
Individual	Gender	Male (*n* = 219)	208.2 (295.8)	< 0.001	63.7 (114.2)	< 0.001	144.5 (224)	**0.001**	2183 (1916.7)	0.248
		Female (*n* = 247)	140.7 (252.1)		38.5 (86.9)		102.2 (195.2)		2170.7 (2374.1)	
	Age	6-11 yr (*n* = 176)	179.1 (276.2)	0.355	43.6 (104)	**0.004**	135.5 (212.8)	0.248	2200.6 (2193.2)	0.831
		12-14 yr (*n* = 147)	164.0 (299.1)		47.0 (101.6)		117.0 (237.6)		2090.5 (2149.9)	
		15-18 yr (*n* = 143)	172.9 (249.1)		62.2 (97.2)		110.7 (174.0)		2235.0 (2170.9)	
	Musculoskeletal disorder	No (*n* = 396)	171.2 (263.1)	0.676	49.4 (101.4)	0.775	121.8 (200.8)	0.421	2249.2 (2170.2)	**0.041**
		Yes (*n* = 70)	179.6 (338.2)		56.0 (101.2)		123.6 (258.1)		1764.9 (2130.5)	
Familial/social	Household	Owner (*n* = 239)	179.7 (250.7)	0.054	57.4 (106.3)	**0.018**	122.2 (185.4)	0.075	2413.6 (1994.4)	**0.008**
		Tenant (*n* = 178)	161.5 (295.1)		42.0 (96.9)		119.5 (225.7)		1994.7 (2415.6)	
		Other (*n* = 24)	138.6 (170.1)		39.2 (59.5)		99.4 (159.7)		2346.2 (2007.6)	
	Child care	Two parents (*n* = 350)	183.7 (286.0)	**0.021**	52.9 (108.3)	0.282	130.8 (216.6)	**0.023**	2205.3 (2121.6)	0.144
		Single parent (*n* = 48)	130.2 (216.1)		41.8 (74.0)		88.4 (172.9)		2093.1 (2189.2)	
		Other (*n* = 10)	53.6 (125.9)		20.0 (43.2)		33.6 (96.2)		1282.0 (2451.6)	
	Father's education	Lower than diploma (*n* = 217)	177.7 (298.1)	0.446	51.5 (104.6)	0.633	126.2 (231.8)	0.233	2098.5 (2151.7)	0.421
		Diploma (*n* = 134)	171.4 (237.4)		39.2 (64.7)		132.23 (194.40)		2442.4 (2266.8)	
		Higher than diploma (*n* = 96)	175.9 (286.8)		68.0 (136.5)		107.9 (185.7)		2215.7 (2104.4)	
	Mother's education	Lower than diploma (*n* = 215)	185.7 (307.1)	0.575	52.9 (112.4)	0.575	132.8 (235.9)	0.552	2175.8 (2399.6)	0.6
		Diploma (*n* = 159)	157.0 (215.0)		41.4 (74.7)		115.6 (173.2)		2215.3 (1901.2)	
		Higher than diploma (*n* = 70)	178.9 (315.7)		64.0 (124.5)		114.8 (217.4)		2256.5 (2108.8)	
	Father's age	< 35 yr (*n* = 22)	140.2 (173.3)	0.367	36.0 (53.8)	0.927	104.1 (151.5)	0.059	1894.1 (1841.9)	0.756
		35-49 yr (*n* = 289)	176.2 (256.7)		49.5 (100.2)		126.7 (198.5)		2239.32 (2106.00)	
		≥ 50 yr (*n* = 135)	179.1 (333.0)		57.1 (115.1)		122.0 (245.7)		2237.8 (2381.8)	
	Mother's age	< 35 yr (*n* = 90)	169.5 (248.4)	0.953	42.0 (80.7)	0.542	127.5 (202.5)	0.759	1863.4 (1888.8)	0.326
		35-49 yr (*n* = 297)	165.6 (252.1)		49.5 (100.0)		116.1 (191.6)		2272.5 (2211.1)	
		≥ 50 yr (*n* = 62)	218.9 (406.3)		69.4 (139.0)		149.5 (297.4)		2278.8 (2403)	

OPA: Organized physical activity; SB: Sedentary behaviors MVPA: Moderate to vigorous physical activities

Table 6 Associations between contributing factors, moderate to vigorous physical activities,and sedentary behaviors in cerebral palsy group

Domain	Variable		MVPA (mins/week)	*P* value	OPA (mins/week)	*P* value	Non-OPA (mins/week)	*P* value	SB (mins/week)	*P* value
Individual	Gender	Male (*n* = 146)	80.9 (163.5)	**0.019**	19.1 (53.5)	**0.045**	61.9 (125.1)	0.107	2236.2 (2531.7)	**0.002**
		Female (*n* = 160)	128.7 (294.4)		33.4 (105.7)		95.3 (260.3)		3098.2 (2740.2)	
	Age	6-11 yr (*n* = 143)	126.4 (288.0)	0.665	23.9 (70.6)	0.681	102.6 (267.5)	0.471	2250.8 (2326.4)	0.076
		12-14 yr (*n* = 82)	98.8 (229.7)		40.5 (130.7)		58.3 (137.6)		3061.3 (2850.2)	
		15-18 yr (*n* = 81)	76.9 (143.5)		17.2 (33.9)		59.7 (127.1)		3078.0 (2963.1)	
	Musculoske-letal disorder	No (*n* = 228)	113.9 (269.2)	0.907	26.8 (83.9)	0.633	87.0 (233.1)	0.976	1771.6 (2807.1)	0.623
		Yes (*n* = 78)	82.7 (131.1)		25.8 (89.1)		56.9 (98.4)		2439.5 (2235.6)	
Familial/social	Household	Owner (*n* = 108)	98.5 (203.5)	0.586	28.0 (85.8)	0.543	70.5 (173.3)	0.418	2411.4 (2769.4)	**0.018**
		Tenant (*n* = 141)	106.8 (248.9)		18.4 (53.4)		88.4 (241.6)		3060.0 (2509.6)	
		Other (*n* = 36)	108.1 (308)		47.1 (150.1)		61.1 (179.3)		221.3 (2841.7)	
	Child care	Two parents (*n* = 242)	115.3 (260.2)	0.828	28.7 (91.0)	0.901	88.6 (227.2)	0.972	2686.2 (2707.5)	0.429
		Single parent (*n* = 25)	60.0 (85.1)		11.6 (21.0)		48.4 (72.0)		3329.4 (2927.9)	
		Other (*n* = 4)	36.3 (66.0)		11.3 (22.5)		25.0 (43.6)		3147.5 (2116.5)	
	Father's education	Lower than diploma (*n* = 122)	114.3 (231.1)	0.182	36.5 (110.3)	**0.029**	77.8 (168.6)	0.257	2879.7 (2684.7)	0.261
		Diploma (*n* = 89)	127.0 (324.4)		21.1 (68.0)		105.9 (311.7)		2847.8 (3060.3)	
		Higher than diploma (*n* = 67)	60.6 (108.2)		14.8 (41.7)		45.8 (89.6)		2199.7 (2229.7)	
	Mother's education	Lower than diploma (*n* = 105)	103.0 (183.5)	0.604	34.7 (99.0)	0.059	68.2 (137.7)	0.908	2514.6 (2757.7)	0.423
		Diploma (*n* = 132)	116.2 (309.6)		22.0 (82.3)		94.2 (279.2)		2967.4 (2822.2)	
		Higher than diploma (*n* = 54)	65.5 (104.8)		17.0 (44.8)		48.5 (86.8)		2642.4 (2291.8)	
	Father's age	< 35 yr (*n* = 24)	99.8 (133.8)	0.117	45.0 (114.2)	0.33	54.8 (73.4)	0.245	2598.5 (2184.7)	0.966
		35-49 yr (*n* = 206)	106.7 (271.1)		22.7 (73.8)		84.0 (240.2)		2711.8 (2839.5)	
		≥ 50 yr (*n* = 51)	103.4 (150.2)		30.7 (108.7)		72.7 (110.4)		2593.2 (2488.7)	
	Mother's age	< 35 yr (*n* = 99)	102.8 (205.7)	0.740	27.4 (84.1)	0.978	75.3 (188.3)	0.802	2829.4 (2773.4)	0.595
		35-49 yr (*n* = 179)	108.2 (264.9)		25 (85.9)		83.1 (226.5)		2639.1 (2696.7)	
		≥ 50 yr (*n* = 16)	40.9 (56.1)		18.4 (35.3)		22.5 (32.0)		3098.4 (2400.9)	

OPA: Organized physical activity; SB: Sedentary behaviors MVPA: Moderate to vigorous physical activities

societies.

In addition, our study showed that among our participants, children with ASD had the highest level of OPA, non-OPA, and total PA, followed by children with ID and then CP. Besides, our study showed that although the pattern and specific type of sedentary behaviors were different among the three groups, children with ASD were similar to ID and better than the CP group. Moreover, regarding the intensity of PA, children with ASD demonstrated the highest levels of moderate and vigorous PA compared to CP and ID groups. Although previous investigations reported a lesser amount of MVPA in children with ASD compared to their TD peers[29,32], our study showed that among two other neurodevelopmental disorders, such as CP and ID, children with ASD would report better results. According to the world health organization (WHO), it is recommended 60 min per day (300 min per week) of MVPA to gain health benefits of PA for children[33]; thus, our study showed that all three groups of participants, on average, participated in less MVPA than what is recommended for children. However, due to the lack of a developed standard of PA or OPA participation for children and adolescents with neurodevelopmental disorders, such interpretation should be made with caution.

To our knowledge, this is one of the first reports representing the amount of OPA/non-OPA as well as sedentary behaviors in children and adolescents with ASD in comparison to other neurodevelopmental disorders such as ID and CP. This finding highlights the importance of considering the health conditions (*e.g.*, motor *vs* non-motor limitation) of children with neurodevelopmental disorders in OPA participating. For example, children with CP might have more motor limitations than children with ASD and ID. Designing adapted OPA specific for each neurodevelopment disorder is of paramount importance for increasing the rate of OPA participation in these populations. As an important limitation, previous studies only examined the general PA participation in ASD and similar disorders. For example, examining ASD with TD peers, data showed an association between lower levels of PA participation and an increase in medical complications such as obesity and chronic illness[11,34]. Recent studies have shown that the issue has worsened because of the COVID-19 pandemic, quarantine, and social distancing[35,36].

Although, according to evidence, the level of PA in children and adolescents with ASD is lower than TD ones, our study showed that, at least in part, the PA status of children and adolescents with ASD is better than other children with neurodevelopmental disorders such as children with CP and ID. It highlights the urgent need to design and develop strategies to enhance the PA and OPA levels for all children and adolescents with neurodevelopmental disorders, which might be challenging due to the lack of studies and the inefficacy of current interventions[37]. This issue warrants much more attention in developing countries which need both increase the general awareness of people and design novel strategies for enhancing adapted PA behavior in individuals with neurodevelopmental disorders. According to theories and frameworks[31], the opportunities for adapted PA/OPA must be intrinsically rewarding to encourage acquiring life skills and reassure peer relationships, parental involvement, and the sense of belonging to a bigger community[38].

Children with CP had the least PA time compared to ASD and ID, possibly related to the higher number of physical and movement incapacities. On the other side, we recruited children and adolescents with ASD from special schools; usually, children who attend these schools are high functioning and consequently do not have the limitations of children with low-functioning ASDs (comorbid with ID and other disabilities). Consequently, they may also have the potential to do more deliberate and regular activities, improving their PA level than more physically and mentally disabling disorders such as CP and ID. Given the above, it seems necessary to develop standards for PA/OPA participation rate in children and adolescents with neurodevelopmental disorders generally and specifically for each group based on the amount of physical and cognitive limitations.

In addition, regarding the contributing factors, our results suggest that gender, parent's education, and childcare status might be related to PA and sedentary behaviors. Factors contributing to enhancing the amount of PA may have an adverse effect on sedentary behaviors and vice versa[39,40]. In the general population, individuals with older age, female gender, comorbidities, the need for movement equipment, or higher BMI are more prone to engage in less PA and more sedentary behaviors[39]. In previous investigations, factors such as symptom severity, gender, having other comorbidities, using mobility equipment, and household status have been reported to contribute to PA participation rate in children with ID and CP[13,14].

The current study is unique in its sample and measures; however, it is not without limitations. The recall bias and the selection of the participants from special schools were from study limitations. In addition, we had to use cross-sectional data for physical activity behavior, and we could not scrutinize the potential effects of data changes over time. Nevertheless, the relatively sizable number of participants could be accounted as one of the important strengths of the current study. This might authenticate and increase the validity of the result in the study despite its limitation.

CONCLUSION

The current study showed that PA behavior in ASD, ID, or CP groups was lower than expected, highlighting the need to support PA/OPA opportunities by designing targeted and adapted programs to decrease unhealthy sedentary behaviors in these groups.

ARTICLE HIGHLIGHTS

Research background

There is little data on physical activity (PA), organized PA (OPA), and sedentary behaviors in children with neurodevel-

opmental disorders in developing countries.

Research motivation

In this large-scale study, we evaluated PA levels among children with neurodevelopmental disorders in the context of a developing country to help identify the groups which benefit the most from the interventions to improve PA levels, which can be a basis for future studies.

Research objectives

To examine OPA, non-OPA, and sedentary behaviors and their associated factors in children and adolescents with autism spectrum disorders (ASD), cerebral palsy (CP), and intellectual disability (ID).

Research methods

A total of 1020 children and adolescents with ASD, CP, and ID living in Tehran between 2011 and 2021 were assessed regarding the child and family information as well as the Children's Leisure Activities Study Survey.

Research results

The results showed that the OPA level was significantly lower than non-OPA in all groups. Moderate to vigorous PA levels were higher among children with ASD compared to children with CP and ID.

Research conclusions

The PA levels are lower than the recommended levels in children with neurodevelopmental disabilities living in a developing country, and there is a need for interventions to improve PA levels, especially OPA, in this group.

Research perspectives

Future studies should focus on evaluating PA levels in children with neurodevelopmental disabilities in other developing countries, and aim to design intervention to improve OPA and total PA in this group.

FOOTNOTES

Author contributions: Memari A was the guarantor; Nakhostin-Ansari A, Shayestehfar M, and Memari A designed and implemented the study; Nakhostin-Ansari A analyzed the data; Nakhostin-Ansari A, Shayestehfar M, Gorgani F, and Hasanzadeh A wrote the initial draft of the manuscript; and all authors read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Influence of resilience on depression among nurses in clean operating departments: The mediating effect of life satisfaction

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Abstract

BACKGROUND

A clean operating room is an important part of surgical and critical treatment in hospitals. The workload is substantial, the pace is rapid, and the working environment is intense; therefore, nurses who work in clean operating rooms are constantly challenged, which can lead to anxiety, depression, and other mental health issues. Life satisfaction and resilience are important factors that ensure mental health. Therefore, exploring the mediating role of life satisfaction in the influence of resilience on depression among nurses in clean operating rooms can help improve nursing services and teamwork.

AIM

To explore the mediating effect of satisfaction on the influence of resilience on depression among nurses in a clean operating department.

METHODS

From April to November 2022, 196 nurses from the Department of Clean Operating at Harbin Medical University Cancer Hospital participated in this study. Participants were selected using convenience sampling. Participants' gender, age, marital status, position, length of service, personal monthly income, daily working hours, employment status, and professional title were collected, and the Connor-Davidson resilience scale, satisfaction with life scale, and self-rating depression scale were used to evaluate resilience, life satisfaction, and depression. The researchers conducted professional training in advance, introduced the research methods to the participants before the investigation, and explained the study's significance and purpose. Surveys were distributed and collected on-site. Each questionnaire took 30 min to complete.

RESULTS

The average scores for life satisfaction, resilience, and depression were 3.13 (±

0.28), 4.09 (± 0.78), and 56.21 (± 8.70), respectively. The correlation between resilience and depression was negative (r = -0.829, P < 0.01). Life satisfaction was positively related to resilience (r = 0.855, P < 0.01) and negatively related to depression (r = -0.778, P < 0.01). The relationship between resilience and depression was partially mediated by life satisfaction. The value of the mediating effect was -6.853 (26.68% of the total effect).

CONCLUSION

Life satisfaction partially mediates the link between resilience and depression among nurses in clean operating departments.

Key Words: Psychological resilience; Depression; Life satisfaction; Clean operation department; Nurses; Mediating effect

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Core Tip: The professional and psychological qualities of clean operating department nurses affect their operation success. Clinical practice emphasizes the importance of the mental health of nurses in operating rooms. This study found that, for nurses working in clean operating departments, resilience was positively correlated with life satisfaction and negatively correlated with depression, indicating that resilience can increase life satisfaction and decrease depression. Life satisfaction mediated the relationship between resilience and depression. This suggests that nurses in clean operating departments should improve their life satisfaction and resilience to adversity to improve their mental health.

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INTRODUCTION

The psychological health of nursing staff has received increasing attention in recent years[1,2]. Relevant studies have shown that heavy, harsh, and demanding working conditions; medical requirements of patients and their families; public opinion; difficulty balancing work and family; salary; and other factors affect the psychological well-being of nursing personnel[3,4]. A clean operating department is necessary for hospitals to provide surgical procedures and treat critically ill patients, and the workload is closely related to the number and difficulty of operations[5,6]. Especially in tertiary hospitals, all types of difficult and complicated diseases are more complex, and new surgical techniques are rapidly being developed. In addition, in clean operating departments, the workload is large, rhythm is fast, and intensity is high□ constantly challenges nurses in clean operating departments, and can easily result in negative emotional states, such as depression and anxiety, and ultimately, psychological problems.

Life satisfaction is the overall cognitive appraisal of a person's level of satisfaction in their life[7]. Life satisfaction is a crucial factor in achieving good mental health and directly associated with various psychological, behavioral, interpersonal, and social factors such as reduced stress, externalized behavior, and internalized problems[8,9]. Therefore, life satisfaction is one of the most important indicators used to gauge an individual's level of happiness and overall quality of life. Further, resilience plays a significant role in positive psychology[10]. Resilience is a psychological quality that allows individuals to cope well with adversity and a protective factor for individual mental health[11,12]. Previous research has reported that life satisfaction is positively associated with individual psychological health and negatively correlated with depression[13,14]. The results of studies conducted with different groups have shown that individual life satisfaction is positively correlated with resilience[15-17].

However, few studies have examined the correlations among resilience, depression, and life satisfaction in nurses in clean operating departments. This study aims to explore the mediating role of life satisfaction in the effects of resilience on depression and to provide a scientific basis for improving resilience, increasing life satisfaction, and reducing the occurrence of depression among nursing staff in clean operating departments.

MATERIALS AND METHODS

Participants

From April to November 2022, 196 nurses from the Department of Clean Operating at Harbin Medical University Cancer Hospital took part in this study. Participants were selected using convenience sampling. The inclusion criteria were as follows: (1) Currently employed on the nursing staff with at least one year of job experience; (2) no personal or family history of mental illness; and (3) no psychotropic drugs use in the last year. The exclusion criteria were as follows: (1) Non-frontline nurses; (2) nurses who took long-term personal, sick, or maternity leave during the study period; (3) nurses

from other departments; (4) nurses participating in other clinical studies; and (5) nurses who were working on an internship or in training.

Basic information survey

The general demographic variables questionnaire designed by this research team was used to collect basic information on the participants, including gender, age, marital status, position, length of service, personal monthly income, daily working hours, employment, and professional title.

Life satisfaction survey

The satisfaction with life scale (SWLS) by Diener *et al*[18] was used to measure life satisfaction. The SWLS includes five items, each rated on a Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). In this study, average scores across the five life satisfaction questions ranged from 1 to 7 points. The SWLS has been shown to be trustworthy and is often utilized in quality-of-life research conducted in Chinese populations[19].

Resilience survey

Resilience was evaluated using the Chinese version of the Connor-Davidson resilience scale (CD-RISC)[20], which has 25 items. Responses were rated on a five-point Likert scale ranging from 0 (never) to 4 (always). The overall scale's average value ranged from 0 to 4, and higher scores indicated greater resilience.

Depression survey

The Self-Rating Depression Scale (SDS), compiled by Zung[21], was used to assess depressive symptoms among the participants in the current or previous week. The scale has 20 questions, 10 positive and negative, rated on a four-point Likert scale (no, sometimes, often, and continuously, rated between 1-4 points respectively). The original score was multiplied by 1.25 to take the integer as the standardized score, and a standardized score > 53 was considered to indicate the presence of depressive symptoms.

Quality control

Prior to beginning the study, the researchers conducted a professional training session in which they introduced the research methods to the participants with unified guidance language and explained the study's significance and purpose. Questionnaires were distributed in person and collected immediately after participants completed them. Participants took approximately 30 min to complete the survey. After eliminating invalid questionnaires, the effective questionnaire recovery rate was 90.8% (178 out of 196). Questionnaire review and score entry was completed by two researchers.

Statistical analysis

Data collected in this study were analyzed using IBM SPSS version 26.0. The significance threshold for each two-sided statistical test was set at $P < 0.05$. The mean, standard deviation (SD), number (n), and percentage (%) were used for descriptive statistics of participant demographics and other factors. A t-test and single-factor analysis of variance were used to compare the variations among classification crowds. Pearson correlation analysis was used to examine the relationship between continuous variables. The mediating effects were examined using Hayes' Process Macro Model 4. To determine whether the regression coefficient of the mediating effect of the estimated chain of 5000 samples in the initial data was significant by employing repeated random sampling, it was determined using a bootstrap 95% confidence interval (CI). If the 95%CI did not contain zero, the indirect effect was considered statistically significant.

RESULTS

Participant characteristics

A total of 196 surveys were distributed, and 178 valid surveys were returned, for a response rate of 90.8%. The participants' ages ranged between 22-52 years, with a mean age of 33.69 years (SD = 6.99). Employment duration ranged between 1-30 years, with a mean of 10.80 years (SD = 7.12). Descriptive statistics are shown in Table 1.

Correlations among resilience, life satisfaction, and depression

Resilience was negatively correlated with depression ($r = -0.829$, $P < 0.01$) and positively correlated with life satisfaction ($r = 0.855$, $P < 0.01$). Life satisfaction was negatively correlated with depression ($r = -0.778$, $P < 0.01$) (Table 2).

Analysis of influencing factors of mental resilience, life satisfaction and depression

As shown in Table 3, the results of multi-factor analysis show that gender, age, working time and employment status are the main factors affecting the level of mental resilience; gender, age and working time are the main factors affecting life satisfaction; gender, age, working time and employment status are the main factors affecting depression score.

Mediating effects of life satisfaction between resilience and depression

In testing the mediating effects, resilience was the independent variable, life satisfaction the mediating variable, and depression the dependent variable. Figure 1 depicts the mediation model established in this study. The regression results

Table 1 Sociodemographic characteristics and their differences among primary variables

Variables		*n*	%	Life satisfaction	Resilience	Depression
				mean ± SD	mean ± SD	mean ± SD
Gender	Male	58	32.58	4.23 ± 0.74	3.25 ± 0.23	53.55 ± 7.10
	Female	120	67.42	4.03 ± 0.79	3.06 ± 0.25	57.50 ± 9.13
	t			2.733	31.112	9.262
	P			0.100	< 0.001	0.003
Age	< 30	60	33.71	4.72 ± 0.82	3.27 ± 0.27	51.47 ± 6.95
	30-45	107	60.10	3.79 ± 0.53	3.06 ± 0.26	58.02 ± 8.31
	46-60	11	6.18	3.60 ± 0.33	2.93 ± 0.22	64.55 ± 8.78
	F			44.439	14.769	19.699
	P			< 0.001	< 0.001	< 0.001
Marital status	Married	104	58.43	3.93 ± 0.65	3.10 ± 0.27	56.86 ± 8.46
	Unmarried	48	26.97	4.55 ± 0.90	3.21 ± 0.29	52.79 ± 7.61
	Divorced or other	26	14.61	3.88 ± 0.67	3.09 ± 0.29	59.96 ± 9.69
	F			13.505	2.829	6.824
	P			< 0.001	0.062	0.001
Educational level	Junior college or below	77	43.26	4.07 ± 0.77	3.11 ± 0.30	56.18 ± 8.99
	University degree or above	101	56.74	4.11 ± 0.78	3.14 ± 0.27	56.24 ± 8.52
	t			0.094	0.566	0.002
	P			0.759	0.453	0.966
Professional title	Primary	54	30.34	4.53 ± 0.88	3.21 ± 0.29	53.11 ± 7.89
	Intermediate	110	61.80	3.92 ± 0.64	3.10 ± 0.26	57.61 ± 8.40
	Senior	14	7.87	3.80 ± 0.68	3.04 ± 0.32	57.21 ± 11.32
	F			14.515	3.738	5.169
	P			< 0.001	0.026	0.007
Years of work experience	< 10	79	44.38	4.51 ± 0.83	3.22 ± 0.27	53.06 ± 7.25
	10-19	74	41.57	3.80 ± 0.55	3.07 ± 0.27	58.07 ± 8.52
	20-38	25	14.04	3.63 ± 0.45	2.98 ± 0.25	60.68 ± 10.15
	F			27.726	9.837	11.328
	P			< 0.001	< 0.001	< 0.001
Monthly income (RMB)	< 3000	39	21.91	4.69 ± 0.88	3.25 ± 0.28	51.46 ± 6.89
	3000-5000	118	66.29	3.94 ± 0.66	3.10 ± 0.27	57.55 ± 8.57
	5001-10000	21	11.80	3.83 ± 0.62	3.05 ± 0.28	57.52 ± 9.73
	F			17.594	5.195	8.034
	P			< 0.001	< 0.001	< 0.001
Daily working hours (h)	< 8	49	27.53	3.83 ± 0.54	3.08 ± 0.26	57.86 ± 9.44
	8-10	129	72.47	4.19 ± 0.83	3.14 ± 0.29	55.59 ± 8.36
	t			7.919	1.694	2.430
	P			0.005	0.195	0.121
Employment status	Formal employee	121	67.98	3.85 ± 0.60	3.08 ± 0.26	58.07 ± 8.72
	Contract employee	57	32.02	4.61 ± 0.85	3.23 ± 0.29	52.26 ± 7.30
	t			46.088	12.488	19.031

P	< 0.001	0.001	< 0.001
Mean	4.09 ± 0.78	3.13 ± 0.28	56.21 ± 8.70

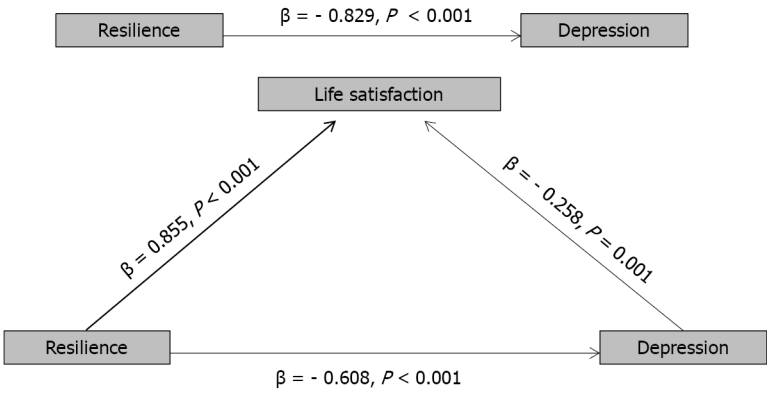
Table 2 Correlations for study variables

Variables	Resilience	Life satisfaction	Depression
Resilience	1		
Life satisfaction	0.855[a]	1	
Depression	-0.829[a]	-0.778[a]	1

[a]*P* < 0.01 (two-tailed), the correlation was significant.

Table 3 Analysis of influencing factors of mental resilience, life satisfaction and depression

Factor	Variables	B	SE	Beta	*t*	*P*
Resilience	Gender	-5.847	0.958	-0.392	-6.101	< 0.001
	Age	-0.861	0.131	-0.857	-6.551	< 0.001
	Daily working hours (h)	-6.947	1.617	-0.443	-4.296	< 0.001
	Employment status	2.297	1.160	0.189	1.979	0.049
Life satisfaction	Age	-0.092	0.011	-0.831	-8.132	< 0.001
	Daily working hours (h)	-0.748	0.176	-0.432	-4.246	< 0.001
	Gender	-0.337	0.104	-0.204	-3.234	0.001
Depression	Age	1.167	0.165	0.937	7.061	< 0.001
	Daily working hours (h)	9.209	2.033	0.474	4.530	< 0.001
	Gender	5.485	1.205	0.296	4.553	< 0.001
	Employment status	-3.422	1.459	-0.227	-2.346	0.02



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Figure 1 The model of the mediating role of life satisfaction in the relationship between resilience and depression.

are presented in Table 4. Resilience had a negative and considerable direct predictive effect on depression (β = -0.608, *P* < 0.001). Further, resilience was found to significantly and positively predict life satisfaction (β = 0.855, *P* < 0.001) and negatively predict depression (β = -0.829, *P* < 0.001). Finally, life satisfaction was found to significantly negatively predict depression (β = -0.258, *P* = 0.001).

As shown in Table 5, the 95%CI of the direct effect of resilience-depression was (-23.636, -14.104), excluding 0, indicating that the direct effect was significant (the value of the effect was -18.832, accounting for 73.32% of the total effect). The 95%CI of the indirect effect of resilience-life satisfaction-depression was (-10.546, -3.120), excluding 0, indicating that life satisfaction mediated the relationship between resiliency and depression (the value of the effect was -

Table 4 Regression analysis of the mediating effect of life satisfaction on resilience and depression

Outcome variable	Predictor variable	*R*	R^2	*F*	β	*t*	*P*
Depression	Resilience	0.829	0.687	385.463	-0.829	-19.633	< 0.001
Life satisfaction	Resilience	0.855	0.732	480.175	0.855	21.913	< 0.001
Depression	Resilience	0.839	0.704	208.553	-0.608	-7.656	< 0.001
	Life satisfaction				-0.258	-3.257	0.001

Table 5 Mediating effect of life satisfaction on resilience and depression

Model pathways	Effect	Boot SE	95%CI		Relative mediation effect, %
			Lower	Upper	
Resilience-life satisfaction-depression	-6.853	1.920	-10.546	-3.120	26.68%
Resilience-depression	-18.832	2.444	-23.636	-14.104	73.32%
Total mediation effect	-25.685	2.515	-23.794	-14.007	-

95%CI: 95% confidence interval.

6.853, accounting for 26.68% of the total effect).

DISCUSSION

The professional and psychological qualities of nurses working in clean operating departments are important factors that affect the success of an operation[22,23]. Maintaining the mental health of nurses in operating departments has become a focus of clinical practice. that the nurses who participated in this study had a mean depression score of 56.21 (± 8.70) points, which exceeded the critical value for the norm score on the Chinese SDS, which is consistent with previous research[24,25]. Clean operating room nurses not only face fast work rhythms and heavy workloads but also need to constantly improve their professional skills[26,27]. In addition, the operating room is an important place to rescue critically ill patients, and surgical nurses often need to complete emergency rescue tasks, which can impact on their mental health.

This study found that, compared with female nurses in clean operating departments, male nurses had higher resilience and life satisfaction scores and lower depression scores, which may be related to gender differences in personality traits. The results also showed that older respondents had lower resilience and life satisfaction scores, and higher depression scores, compared with younger respondents. This may be due to older nurses often being required to deal with more complex work because of their rich work experience, resulting in increased work pressure and, subsequently, more psychological difficulties. Regarding marital status, the findings showed that, compared with unmarried nurses, nurses whose marital status was married, divorced, or other had lower resilience scores and higher depression scores. This may be because married nurses tend to receive family support and help, and can often obtain psychological comfort in their marriage. This study further found that, compared with nurses with intermediate and senior professional titles, those with junior professional title had lower resilience and life satisfaction scores and higher depression scores. This may be related to the fact that pressure to receive a promotion often negatively affects the mental health of those with low-level professional titles. In this study, compared to nurses with less than ten years of work experience, those in the groups with 10-19 or 20-38 years of work experience had lower resilience and life satisfaction scores and higher depression scores. This may be because nurses with extensive work experience have experienced more problems that can arise in emergency surgery, high-risk patients, medical problems, and job promotions, resulting in greater psychological pressure. Compared with those with a personal monthly income < 3000 yuan, nurses with a personal monthly income of 3000-5000 yuan or 5001-10000 yuan had lower resilience and life satisfaction scores and higher depression scores, which may be related to higher income indicating more job requirements, promotion pressure, and family expectations. In addition, compared with contract nurses, formal nurses had lower resilience and life satisfaction scores and higher depression scores. This may be because formal nurses must deal with administrative work while also completing nursing work and face a more stringent assessment mechanism.

This study found that resilience among the participants was positively correlated with life satisfaction scores and negatively associated depression scores. This indicates that, among nurses working in clean operating departments, the better the resilience, the greater the life satisfaction and lower the depression, which is in accordance with the findings of previous studies[28,29]. Good resilience and life satisfaction are indicators of less psychological difficulty. As a protective factor for adversity, resilience can mobilize individuals to use their own strengths and resources, mitigate the negative impact of risk factors, and ultimately reduce the probability of negative consequences while increasing that of positive

outcomes. These positive outcomes will increase life satisfaction, so that the individual's cognition of people and things related to it is more positive. In addition, nurses will have more positive experiences in life, work, and study, resulting in a decreased risk for psychological problems[30,31].

This study's findings indicate that the connection between resilience and depression is partially mediated by life satisfaction among nurses working in a clean operating department. The value of the effect was -6.853, accounting for 26.68% of the total effect. Related studies have shown that the higher an individual's resilience, the higher their life satisfaction, and high life satisfaction indicates good mental health and low depressive symptoms[32,33]. One characteristic of highly resilient individuals is that they can maintain a high level of life satisfaction in a complex environment, and the positive emotional experience generated by high life satisfaction reduces depression[34,35]. In view of the psychological status of nurses in the operating room, hospitals should regularly carry out psychological and physiological assessment activities for nurses in the operating room, understand the source of stimuli and the causes of nurses' depression, and carry out targeted intervention measures to help nurses decompress psychologically, relieve fatigue and boredom, and improve their life satisfaction and psychological resilience. At the same time, the hospital should further deepen the reform of management mode, establish the professional ethics of medical staff, stimulate the enthusiasm and standardization of nurses' work, and create a good working atmosphere. In addition, we suggest that the hospital actively take targeted intervention measures to optimize the working state of nurses by improving their psychological quality and mental resilience, and finally improve their life satisfaction. For example, experts are invited to hold lectures regularly, and nurses are trained to endure hardships and overcome setbacks through practical experience or typical cases. Psychological lectures, cognitive behavior intervention, relaxation training and other activities were carried out for nurses to help them improve their physical and mental state, psychological resilience and life satisfaction.

However, several factors can affect the mental health of nurses in clean operating departments, such as work boredom, work pressure, job burnout, and lack of social support. This study selected only one direction for in-depth discussion, which is a limitation. In future studies, we hope to further analyze other factors. To improve the mental health of nurses in clean operating departments to provide a more reliable theoretical basis.

CONCLUSION

Depression scores were negatively correlated with resilience. Life satisfaction was positively related to resilience and negatively related to depression. The connection between resilience and depression was partially mediated by life satisfaction among nurses working in a clean operating department.

ARTICLE HIGHLIGHTS

Research background

A clean operating department is important for hospitals to implement surgical treatments and attend to critically ill patients. These departments have a large workload, fast rhythm, and high intensity. The working environment in clean operating departments constantly challenges nurses and can easily lead to negative mental states, such as despair and anxiety, and ultimately, psychological problems. However, ensuring the mental health of nurses in clean operating departments is key to the normal functioning of hospital operating rooms.

Research motivation

A crucial determinant of a person's subjective well-being and quality of life is their level of life satisfaction. Resilience is a protective factor for individual mental health. Both are important factors in ensuring mental health. Therefore, exploring the mediating role of life satisfaction in the effects of resilience on depression among nurses in clean operating departments can provide a reference for promoting harmonious development among nursing teams in operating rooms and improving the quality of nursing services.

Research objectives

To investigate how depression and resilience are related and the possible mediating role of life satisfaction in this association among nurses in clean operating departments and provide a scientific basis for increasing their resilience and life satisfaction, and reducing the occurrence of depression.

Research methods

A total of 196 nurses from three clean operating departments in one hospital were selected using convenience sampling. The Connor-Davidson resilience scale, satisfaction with life scale, and self-rating depression scale (SDS) were used to evaluate resilience, life satisfaction, and depression.

Research results

The mean depression score for nurses in the clean operating department was 56.21 (± 8.70), which exceeded the critical value of the norm score for the Chinese SDS. Nurses' resilience was positively correlated with life satisfaction and negatively correlated with depression. Life satisfaction served as a partial mediator between resilience and depression in

the nurses in the clean operating department, with a mediation effect value of -6.853, accounting for 26.68% of the total effect.

Research conclusions

Life satisfaction had a partial mediating role between resilience and depression among nurses in a clean operating department, suggesting that hospitals should not only increase the resilience of medical staff in the face of adversity but also promote the mental health level of this group by improving their life satisfaction.

Research perspectives

Depression is not the only psychological problem that nurses in clean operating departments face. In the future, we will further study psychological distress and its influencing factors among nurses in clean operating departments to provide a more reliable theoretical basis for ensuring their mental health.

FOOTNOTES

Author contributions: Gao G and Shen XF contributed to study concepts and study design; Li L, Ma H, and Liu J contributed to data acquisition and data analysis; Jin LW, Li X, and Wang JS contributed to literature research.

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Informed consent statement: Written informed consent was obtained from all participants.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Data sharing statement: The raw data supporting the conclusions of this study will be made available by the corresponding author.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Effect of CICARE communication nursing model combined with motivational psychological intervention in patients with post-intensive care unit syndrome

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Abstract

BACKGROUND

Post-intensive care syndrome (PICS) is a term used to describe a constellation of new or worsened dysfunctions in the physical, cognitive, or mental health status of critically ill patients after their discharge from the intensive care unit (ICU). These dysfunctions persist beyond the acute phase of illness and have a significant impact on both the patient and their family. Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication advocates that patients should be respected and accepted when receiving medical services. Clinicians should attach importance to the communication mode of feelings, including connection, introduction, communication, ask, response, and exit 6 steps.

AIM

To assess the impact of CICARE communication on the reduction of anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms in patients transitioning from the ICU to other care settings.

METHODS

This prospective, randomized, controlled study was performed between October 2021 and March 2023. Intensive Care Unit Memory Tool was used to evaluate patients' ICU memory. The Hospital Anxiety and Depression Scale was employed to determine the presence of anxiety or depression symptoms. Impact of Event Scale-Revised was utilized to assess the presence of PTSD. All data were processed and analyzed using R language software version 4.1.0. The measurement data were expressed as mean ± SD, and the *t* test was used. The count data were analyzed by the χ^2 test and expressed as [*n* (%)].

RESULTS
In total, 248 subjects were included in this study. Among them, 206 were successfully followed up for three months after transfer from the ICU, and 42 cases were lost to follow-up. There was no significant difference in the composition of ICU memory between the two groups. The application of the CICARE communication nursing model combined with the motivational psychological intervention nursing model, as well as the adoption of only the motivational psychological intervention nursing model, demonstrated favorable effects on PICS. Both groups of patients showed a reduction in anxiety scores, depression scores, and PTSD scores following the implementation of these two nursing models. However, it is noteworthy that the experimental group exhibited greater improvements compared to the control group.

CONCLUSION
Our findings suggest that CICARE communication nursing mode may have good influence on relieving PICS.

Key Words: Connect, Introduce, Communicate, Ask, Respond, Exit; Post-intensive care syndrome; Motivational psychological intervention

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Core Tip: Post-intensive care syndrome (PICS) is a series of new or aggravated dysfunctions in the physical, cognitive or mental health status of a critically ill patient after discharge from intensive care unit. Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication advocates that patients should be respected and accepted during the provision of medical services. CICARE communication nursing mode may have good influence on relieving PICS.

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INTRODUCTION

Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication is an approach that emphasizes the respect, acceptance, and acknowledgement of patients during the delivery of medical services. It places importance on the effective communication of emotions, encompassing six key steps: Connect, introduce, communicate, ask, respond, and exit. Research has shown that under the clear guidance of these steps, patients' satisfaction with health care has been improving[1]. For example, the application value of CICARE communication mode nursing intervention in patients with coronary artery disease after percutaneous coronary intervention has demonstrated notable value. It has shown great potential in reducing disease uncertainty, improving treatment adherence, enhancing patients' self-care abilities, and promoting both quality of life and nursing satisfaction[2].

With the development of modern technology and medical technology, intensive care unit (ICU) treatment technology has rapid development, including advanced respiratory and circulation acquired immunodeficiency syndrome, a variety of standard diagnosis and treatment guidelines, the implementation of health education programs, so that the short-term results of ICU patients, including mortality rates and 28-d survival rates, there has been a significant increase[3]. However, the long-term prognosis and quality of life of sepsis patients remains poor, and there are many studies showings that some patients transferred out of ICU may be suffer from cognitive, mental, and physical impairments are common in patients transferred out of ICU, which can last for months or even years, or remission over time and this syndrome is called post-intensive care syndrome (PICS) which is a range of cognitive, mental, and physical impairments that are new or increased in critically ill patients after transfer from ICU and continue to affect the patient after discharge; or because of the patients admitted to ICU for treatment and late care, the family members brought a variety of pressure, resulting in psychological and physical disorders[4-7].

Numerous studies have focused on developing strategies to reduce the risk of PICS, and caregivers of PICS. High levels of education and early active mobilization are considered potential risk factors for PICS[8-11]. The impact of nursing interventions on PICS is an area that has been inadequately explored in the existing literature. Specifically, the influence of CICARE communication on PICS remains largely understudied. In light of this knowledge gap, our study aimed to evaluate the potential effects of CICARE communication on the duration of post-ICU stay, as well as its impact on anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms among patients transitioning from the ICU to other care settings.

MATERIALS AND METHODS

Research contents

This prospective, randomized, controlled study was performed between October 2021 and March 2023 in Department of Neurosurgery, Dushu Lake Hospital Affiliated to Soochow University. The study was registered at the Clinical Trial Center (www.researchregistry.com) with registration number (researchregistry9376). All subjects have signed the consent form before participating in the study. Patients were divided into two groups, experiment group and controlled group. The patients of experiment group received the CICARE communication nursing model combined with motivational psychological intervention nursing model, and the patients of controlled group received the motivational psychological intervention nursing model. The main study objective was to investigate differences in the occurrence of symptoms of anxiety, depression and PTSD at 3 mo after ICU transfer between two groups of patients receiving different modes of nursing care.

Patient selection

Patients hospitalized and successfully transferred out of comprehensive ICU were selected as subjects by convenience sampling. All patients seen by the investigators in their clinical practices or who responded to requests for volunteers were screened for participation in the study. Those who met the screening criteria and gave their consent were sequentially admitted. Inclusion criteria: (1) At least 18 years old; (2) ICU stay longer than 24 h; (3) Patients transferred to the general ward after ICU treatment; and (4) Informed consent and voluntary participation in the study. Exclusion criteria: (1) Patients with severe brain injury or brain disease; (2) Patients with cognitive dysfunction; (3) Patients with language dysfunction and inability to communicate effectively; (4) Patients transferred to ICU twice or more; (5) Patients with mental disorders; and (6) Patients with malignant diseases receiving palliative care.

Materials

General information questionnaire: The general information questionnaire included gender, age, education, length of stay in ICU, diagnosis of ICU admission, presence of sepsis during ICU treatment, presence of hormones, and presence of analgesics. Intensive Care Unit Memory Tool (ICUMT): The ICUMT, assessment of patients' ICU memory, consists of a total of 14 questions: 5 open-ended questions and 9 closed questions. It mainly includes three parts: (1) The memory of admission and ICU transfer; (2) The memory during ICU care was divided into three dimensions, a total of 21 items: Factual memory (family, face, darkness, alarm sound, breathing tube, clock, sound, sputum aspiration, nasal cannula, light, medical rounds); delusional memories (others wanting to harm themselves, hallucinations, nightmares, dreams); emotional memory (discomfort, confusion, low mood, anxiety and panic, panic, pain); and (3) Memory after transfer out of ICU and ICU[12].

The Hospital Anxiety and Depression Scale (HADS): HADS was divided into two subscales of anxiety and depression, with a total of 14 items, among which 7 items (A) assessed anxiety and 7 items (D) assessed depression, and each item was scored at four levels of 0-3. The subscale was divided into critical value with 8 points, 0-7 points indicated no symptoms, and 8-10 points indicated possible anxiety or depression. A score of 11 to 21 indicates the presence of anxiety or depression symptoms, and the higher the score, the more severe the anxiety or depression symptoms[13,14].

Impact of Event Scale-Revised (IES-R): IES-R consists of 22 entries, including the three core symptoms of PTSD: Intrusion, avoidance and increased alertness were scored on five levels ranging from 0 (never) to 4 (always), with a total score ranging from 0 to 88, and a critical value of 35. The total score ≥ 35 was classified as positive PTSD symptoms, and the higher the score, the more serious the PTSD symptoms[15].

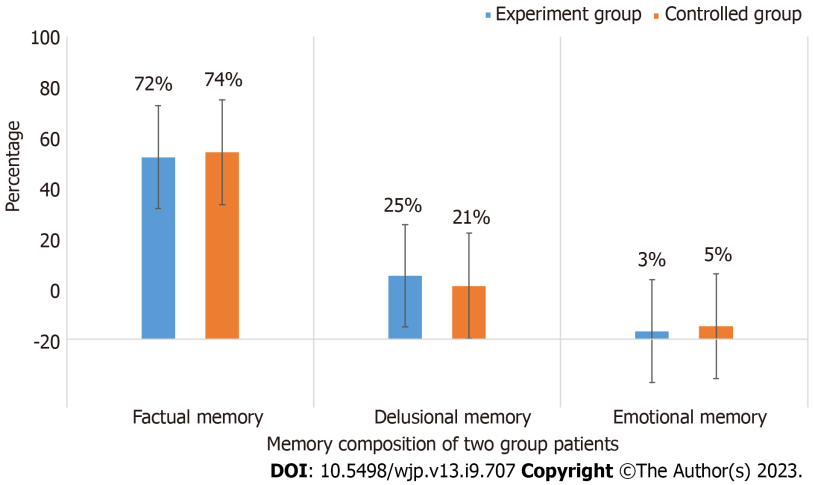
Within one week after the patients were transferred from ICU to the general ward (with appropriate extension to two weeks for special patients), the researchers visited the ward for follow-up, and reported. After knowing the purpose and significance of the study, the informed consent was signed after obtaining the informed consent of the patients, and the general information questionnaire and ICU memory assessment scale were distributed. For the patients who could not complete the questionnaire independently, the questionnaire contents were read aloud word by word, and the patients provided oral answers, and the researchers filled in the answers for them. HADS and IES-Rs were collected by telephone interview at 3 mo after patients were transferred out of the ICU. The questionnaire was read aloud, word for word, and the patients responded verbally, while the researchers wrote the answers for them. Limit each phone interview to 15 to 20 min.

Statistical analyses

The integrity of all questionnaires was checked before input, and invalid questionnaires with obvious logical contradictions or too many missing items were eliminated. All data were processed and analyzed using R language software version 4.1.0. The measurement data were expressed as mean ± SD, and the t test was used. The count data were expressed as [n (%)], and the χ^2 test was used. $P < 0.05$ was considered statistically significant.

RESULTS

There were 248 subjects were included in this study, and 206 patients were successfully followed up three months after being transferred out of ICU, and 42 cases were lost to follow-up from October 2021 and March 2023. The reasons for the loss of follow-up included death, refusal to participate in the investigation, loss of contact, and failure to cooperate with



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Figure 1 Intensive care unit memory composition of two group patients.

the investigation in critical condition. Among 206 patients successfully followed up, 125 (60.7%) were male and female in 81 cases (39.3%); most of the patients were over 45 years old, with 112 cases (54.4%), which were presented in Table 1.

There was no statistical difference in the composition of ICU memory between the two groups, and 72% of patients in the experimental group had factual memory. Delusional memory was present in 25% of patients and emotional memory was present in 3%; in the control group, 74% of patients had factual memories, 21% had delusional memories, and 5% had emotional memories (see Figure 1). There was no statistic difference in ICU memory composition of two group patients.

HADS and IES-R score change of two group patients were presented in Table 2. Adopting CICARE communication nursing model combined with motivational psychological intervention nursing model and only adopting motivational psychological intervention nursing model both had good influence on PICS. Anxiety score, depression score and PTSD score of both group patients decreased after using these two nursing modes, but experiment group was better than the control group.

DISCUSSION

Annually, a staggering number of over 20 million patients worldwide necessitate ICU treatment due to severe illness, injury, or the worsening of chronic conditions. Advances in medical technology have increased the survival of critical illness, increasing the number of patients transferred out of the ICU, and increasing attention to their long-term outcomes [16,17]. Patients may experience both physiological and psychological stressors during their stay in the ICU, including critical illness, sedation, pain, sleep deprivation, noise, delirium, lack of privacy, and fear. These experiences can significantly impede the recovery process and may even contribute to the development of psychological disorders, including anxiety, depression, and PTSD, following the patient's discharge from the ICU. Among these, anxiety, depression, and PTSD are the most prevalent psychological conditions observed in such cases[18]. According to the above facts, The American Academy of Critical Care Medicine Put forward the concept of PICS that it is a series of new or aggravated dysfunction in the physical, cognitive or mental health status of a critically ill patient after discharge, which continues to affect the patient or his or her family. There are many studies on the influencing factors of psychological disorders in patients transferred out of ICU, mainly focusing on demographic factors (such as gender, age, education level, family income, *etc.*), disease factors (such as chronic history, severity of disease, sepsis, *etc.*), and factors related to ICU treatment (such as the use of glucocorticoids, the use of analgesics, the use of sedatives, *etc.*). It is a great challenge for intensive care to improve long-term mental health and health-related quality of life of patients transferred out of ICU.

CICARE communication mode is a process-oriented communication approach advocated by American medical institutions. It integrates psychological and medical knowledge along with humanistic values to enhance the effectiveness of communication between healthcare providers and patients in outpatient settings. The implementation of CICARE communication mode aims to improve patients' medical experience and enhance the overall quality of care delivery. In our study, 14 nurses were trained in CICARE communication mode for 1 mo and passed the examination. CICARE mode was fully applied in the experiment group patients who accepted the motivational psychological intervention at same time. After study and observation, the experiment patients more willing to speak out their demand and worries. Other studies have found the same thing[2,19-21]. CICARE communication is a mode of communication that advocates good communication that attends to the patients feelings of being respected, accepted and valued during the provision of medical services for patients, including connect, introduce, communication, ask, response and exit. Patients feel respected and are more likely to trust their doctors, talk about their problems, and give feedback. A major limitation of this study is that we enrolled a small sample size from a single-center study. Therefore, our results may not be generalized.

Table 1 Baseline characteristics of subjects

	Indicator	Number	Percentage
Gender	Male	125	60.7
	Female	81	39.3
Age (yr)	< 30	27	13.1
	30-45	67	32.5
	> 45	112	54.4
Operation situation	Non-operation	38	18.4
	Elective operation	102	49.5
	Emergency	66	32.1
Length of ICU stay	1-5	123	59.7
	5-10	55	26.7
	10-20	14	6.8
	> 20	14	6.8
Tranquilizer	Yes	181	87.9
	No	25	12.1
Sedative	Yes	166	80.6
	No	40	19.4

ICU: Intensive care unit.

Table 2 Hospital Anxiety and Depression Scale and Impact of Event Scale-Revised score change of two group patients

	Experiment group	Controlled group
Samples	103	103
Anxiety score	12	11
Depression score	10	9
PTSD score	52	52
ICU transfer anxiety score at three months	3	6
Depression score at three months after ICU transfer	2	5
PTSD score at three months after ICU transfer	16	38

PTSD: Post-traumatic stress disorder; ICU: Intensive care unit.

CONCLUSION

CICARE communication nursing mode may have good influence on relieving PICS. Patients transferred from ICU can be adopted CICARE communication nursing model combined with motivational psychological intervention nursing model, rather than only motivational psychological intervention nursing model.

ARTICLE HIGHLIGHTS

Research background

Connect, Introduce, Communicate, Ask, Respond, Exit (CICARE) communication is a kind of advocating that patients should be respected, accepted and accepted when providing medical services attach importance to the communication mode of feelings. Post-intensive care syndrome (PICS) is a series of new or aggravated dysfunction in the physical, cognitive or mental health status of a critically ill patient after discharge, which continues to affect the patient or his or her family.

Research motivation

The aim of this study was to evaluate CICARE communication whether shorten post-intensive care (ICU), affecting anxiety, depression, and post-traumatic stress disorder (PTSD) in patients transferred out of the ICU.

Research objectives

The object of this study as follows: (1) Assess the impact of CICARE communication combined with motivational intervention on anxiety, depression, and PTSD symptoms in PICS patients; (2) Compare outcomes between CICARE + motivational intervention and motivational intervention alone; and (3) Determine feasibility and acceptability of implementing CICARE communication in PICS care.

Research methods

The study employed a prospective, randomized, controlled design. Data collection occurred from October 2021 to March 2023. ICU memory was evaluated using the Intensive Care Unit Memory Tool. Anxiety and depression symptoms were assessed using Hospital Anxiety and Depression Scale, while PTSD was measured with Impact of Event Scale-Revised. Statistical analysis utilized R software (version 4.1.0). Follow-up was conducted for three months after ICU transfer.

Research results

There was no statistical difference in the composition of ICU memory between the two groups. Adopting CICARE communication nursing model combined with motivational psychological intervention nursing model and only adopting motivational psychological intervention nursing model both had good influence on PICS. Anxiety score, depression score and PTSD score of both group patients decreased after using these two nursing modes, but experiment group was better than the control group.

Research conclusions

CICARE communication nursing mode may have good influence on relieving PICS.

Research perspectives

Patients transferred from ICU can be adopted CICARE communication nursing model combined with motivational psychological intervention nursing model, rather than only motivational psychological intervention nursing model.

FOOTNOTES

Author contributions: She SJ and Xu YY contributed equally to this work; Xu YY designed the study; She SJ contributed to the analysis of the manuscript; She SJ and Xu YY involved in the data and writing of this article; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Dushu Lake Hospital Affiliated to Soochow University Institutional Review Board.

Clinical trial registration statement: The study was registered at the Clinical Trial Center (www.researchregistry.com) with registration number (researchregistry9376).

Informed consent statement: All subjects have signed the consent form.

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ORIGINAL ARTICLE

Case Control Study

Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalogram slow wave/fast wave frequency ratio in epilepsy

Xiao-Fen Huang, Ming-Xia Xu, Yue-Fan Chen, Yun-Qing Lin, Yuan-Xiang Lin, Feng Wang

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Abstract

BACKGROUND

Cognitive dysfunction in epileptic patients is a high-incidence complication. Its mechanism is related to nervous system damage during seizures, but there is no effective diagnostic biomarker. Neuronal pentraxin 2 (NPTX2) is thought to play a vital role in neurotransmission and the maintenance of synaptic plasticity. This study explored how serum NPTX2 and electroencephalogram (EEG) slow wave/fast wave frequency ratio relate to cognitive dysfunction in patients with epilepsy.

AIM

To determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in epilepsy patients.

METHODS

The participants of this study, conducted from January 2020 to December 2021, comprised 74 epilepsy patients with normal cognitive function (normal group), 37 epilepsy patients with cognitive dysfunction [epilepsy patients with cognitive dysfunction (ECD) group] and 30 healthy people (control group). The mini-mental state examination (MMSE) scale was used to evaluate cognitive function. We determined serum NPTX2 levels using an enzyme-linked immunosorbent kit and calculated the signal value of EEG regions according to the EEG recording. Pearson correlation coefficient was used to analyze the correlation between serum NPTX2 and the MMSE score.

RESULTS

The serum NPTX2 level in the control group, normal group and ECD group were 240.00 ± 35.06 pg/mL, 235.80 ± 38.01 pg/mL and 193.80 ± 42.72 pg/mL, respectively. The MMSE score was lowest in the ECD group among the three, while no significant difference was observed between the control and normal groups. In epilepsy patients with cognitive dysfunction, NPTX2 level had a positive correlation with the MMSE score (r = 0.367, P = 0.0253) and a negative correlation with epilepsy duration (r = −0.443, P = 0.0061) and the EEG slow wave/fast wave frequency ratio value in the temporal region (r = −0.339, P = 0.039).

CONCLUSION

Serum NPTX2 was found to be related to cognitive dysfunction and the EEG slow wave/fast wave frequency ratio in patients with epilepsy. It is thus a potential biomarker for the diagnosis of cognitive impairment in patients with epilepsy.

Key Words: Serum neuronal pentraxin 2; Cognitive dysfunction; Epilepsy; Electroencephalogram slow wave/fast wave frequency ratio; Biomarker

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Core Tip: Here, we found serum neuronal pentraxin 2 (NPTX2) levels were found to be significantly higher in the normal group than in the cognitive dysfunction group. Additionally, NPTX2 levels showed a positive correlation with cognitive function scores and a negative correlation with epilepsy duration and electroencephalogram (EEG) slow wave/fast wave frequency ratio values in the temporal region. Serum NPTX2 level and the EEG slow wave/fast wave frequency ratio value had good sensitivity and specificity for evaluating cognitive dysfunction. These findings suggest that serum NPTX2 could be a valuable biomarker for diagnosing cognitive impairment in patients with epilepsy, providing important insights for clinical practice.

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INTRODUCTION

Epilepsy is a common neurological disorder characterized by abnormal synchronous firing of neurons in the brain[1]. The causes of epilepsy are sometimes known and sometimes unknown (idiopathic epilepsy). Epidemiological studies have shown that approximately 70% of adults with epilepsy have cognitive dysfunction[2,3]. However, there are no effective cognitive assessment criteria for patients with epilepsy. Cognitive dysfunction in epilepsy patients occurs on multiple levels, including executive ability, attention, language, and memory ability. Various epilepsy-related factors are closely related to cognitive dysfunction, including epilepsy course, lesion location, underlying neuropathology, and antiepileptic seizure drugs[2]. Cognitive impairment is common in epileptic patients and is characterized by impairment in neurological function. Due to the lack of early diagnostic methods for cognitive impairment in epilepsy patients, unavoidable neurological damage is present in epilepsy patients[3,4].

Neuronal pentraxin 2 (NPTX2), also named "neuronal activity-regulated pentraxin", is first find in in 1995[5]. NPTX2 is being found to take part in neurotransmission, the maintenance of synaptic plasticity, and the formation of excitatory synapses at presynaptic and postsynaptic sites[6,7]. NPTX2 is also being found to take part in Parkinson's disease[8,9], ischemic diseases[10,11], and Alzheimer's disease[12,13]. A recent study reported that NPTX2 was a novel biomarker for Alzheimer's disease[14]. In addition, researchers have explored the role of NPTX2 in vascular dementia. A recent study reported significantly higher serum levels of NPTX2 in patients with vascular dementia than in healthy controls. Furthermore, NPTX2 serum levels were found to be significantly correlated with cognitive function scores in patients with vascular dementia[15]. However, we still known nothing about NPTX2 in epilepsy.

This study evaluated NPTX2 serum levels in epilepsy patients, and future study their relationship with the patients' cognitive function.

MATERIALS AND METHODS

Patients and ethical statement

This study enrolled 111 patients diagnosed with epilepsy at the First Affiliated Hospital of Fujian Medical University between January 2020 and December 2021. In addition, 30 healthy volunteers were recruited as a control group. The

inclusion criteria were as follows: (1) Clinically confirmed epilepsy [electroencephalogram (EEG) with or without epileptiform discharge]; (2) No seizures 24 h before enrollment; (3) Age between 18 and 60 years; (4) Clear consciousness and cooperative during the examinations; (5) Normal vision, hearing, and speech functions; (6) An education level of at least primary school and an ability to understand the scale content sufficiently to answer the questions; (7) Signed an informed consent form; and (8) Asymptomatic epilepsy (head computed tomography or magnetic resonance imaging does not show intracranial lesions). The exclusion criteria were as follows: (1) Liver dysfunction (alanine transaminase or aspartate aminotransferase > 50 U/L) or renal impairment (serum creatinine > 135 μmol/L); (2) In the acute stage of the disease course; (3) A long-term history of alcoholism or psychoactive substance abuse or recent use of drugs that could affect cognitive function such as antidepressants, antipsychotics, baclofen, and benzodiazepines; or (4) Uncooperative behavior. The study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the ethics board of the First Affiliated Hospital of Fujian Medical University (No. [2019]274). Informed consent was obtained from all participants.

Cognitive function assessment

The mini-mental state examination (MMSE) scale was used to evaluate cognitive function in all participants. The MMSE scale consists of 30 questions related to cognitive function; each correct answer receives one point. An MMSE scale score of less than 27 indicates cognitive dysfunction in persons with at least a junior high school education[16].

Serum NPTX2 assay

Fasting venous blood was drawn from all participants. The peripheral blood was centrifuged at room temperature to obtain serum, which was then frozen in liquid nitrogen, awaiting further tests. Serum NPTX2 was detected using a Human Neuronal pentraxin-2 (NPTX2) enzyme-linked immunosorbent assay kit (CSB-EL016030HU; CUSABIO, Houston, TX, United States).

EEG test

All patients with epilepsy were subjected to an EEG test. The test was conducted in a quiet room, and the patients were told to relax and stay awake with closed eyes. The patients were also subjected to induction tests such as opening their eyes and hyperventilation. The EEG detection parameter settings were as follows: Filter channel 0.5–30 Hz, time constant 0.3, paper feed speed 3 cm/s, gain 100 μV = 1 cm, and scalp resistance of each electrode not exceeding 5,000 Ω. After selecting monopolar lead tracing for 1 min and once the EEG signal was stable, the EEG signal sampling without artifacts and representing EEG background activity was selected. Each patient took 8 s for one sampling unit, with 10 sampling units selected intermittently. The EEG slow wave/fast wave frequency ratio (EEGs value) was calculated using the fast Fourier transform method: EEGs value = (δ+θ)/(α1+α2+β1+β2). δ (1.0–3.9 Hz), θ (4.0–7.9 Hz), α1 (8.0–10.0 Hz), α2 (10.1–13.9 Hz), β1 (14.0–19.9 Hz), and β2 (20.0–30.0 Hz).

Statistical analysis

Data were recorded in an Excel sheet and were analyzed using SPSS 25.0 (IBM, Corp., Armonk, NY, United States). Count data were expressed as percentages, while continuous data were expressed as mean ± SD. The Kolmogorov–Smirnov test was used to test whether the quantitative data were normally distributed. Normally distributed data were presented as (mean ± SD), and differences between groups were analyzed using unpaired Student's *t*-test. Non-normally distributed quantitative data were presented as the median (interquartile range), and differences between groups were analyzed using the Mann–Whitney U-test. The Pearson correlation coefficient was used to analyze the correlation between two variables of measurement data. Furthermore, the receiver operating characteristic curves were constructed, and the area under the curve (AUC) was calculated to assess the performance of NPTX2 serum levels and EEGs values in diagnosing cognitive dysfunction in patients with epilepsy. A P value < 0.05 was considered statistically significant.

RESULTS

Cognitive function and baseline data of patients with epilepsy

Cognitive function was assessed using the MMSE scale. The epilepsy patients with cognitive dysfunction (ECD) group recorded the lowest MMSE score among the three groups. Furthermore, no significant difference in MMSE scores was observed between the control and normal groups (P > 0.05, Figure 1). In addition, the age, gender, education and something related to epilepsy between normal group and ECD group are omparable (P > 0.05, Table 1).

Relationship between NPTX2 serum levels and clinical features

No statistically significant difference was observed in NPTX2 serum levels between the control and normal groups (P > 0.05). However, serum NPTX2 levels in normal group were significantly higher than that in the ECD group (P < 0.05, Figure 2). The serum level of NPTX2 was positively related to MMSE score (r = 0.367, P = 0.0253), not to age (r = 0.115, P = 0.497), and negatively related to epilepsy duration (r = -0.443, P = 0.0061, Figure 3) in the ECD group. In addition, no significant differences were found in gender, education level, epilepsy type, epilepsy drug types, or treatment protocol between the ECD and normal groups (Figure 4).

Table 1 Baseline data for epilepsy patients with different cognitive function and healthy volunteers

Variable	Control (*n* = 30)	Epilepsy		*P* value	
		Normal (*n* = 74)	ECD (*n* = 37)	*P*[1]	*P*[2]
Age (yr, mean ± SD)	33.93 ± 9.39	35.27 ± 9.73	34.68 ± 9.50	0.523	0.760
Gender, *n* (%)					
Male	17	48 (64.86)	20 (54.05)	0.434	0.270
Female	13	26 (35.14)	17 (45.95)		
Education level, *n* (%)					
Junior/senior high school	19	46 (62.16)	20 (54.05)	0.911	0.412
University or above	11	28 (27.84)	17 (45.95)		
Epilepsy onset age (yr, mean ± SD)	–	26.15 ± 7.41	25.62 ± 10.52	–	0.760
Epilepsy duration (yr, mean ± SD)	–	9.12 ± 5.60	9.05 ± 4.10		0.948
Epilepsy type, *n* (%)					
Focal	–	20 (27.03)	9 (24.32)	–	0.760
Overall	–	54 (72.97)	28 (75.68)		
Types of epilepsy drugs, *n* (%)					
0–1	–	57 (77.03)	26 (70.27)	–	0.440
2–3	–	17 (22.97)	11 (29.73)		
Epilepsy treatment protocol, *n* (%)					
VPN	–	39 (52.70)	19 (51.35)	–	0.890
No-VPN	–	35 (47.30)	18 (48.65)		

[1]Control group *vs*. epilepsy (normal) group.
[2]Epilepsy (normal) group *vs*. epilepsy patients with cognitive dysfunction group.
ECD: Epilepsy patients with cognitive dysfunction; VPN: Valproate.

Table 2 Comparison of electroencephalogram slow wave/fast wave frequency ratio for different brain regions of epilepsy patients with different cognitive function (mean ± SD)

Area of ECG	Epilepsy		*t*	*P*
	Normal (*n* = 74)	ECD (*n* = 37)		
Frontal region	0.54 ± 0.20	0.65 ± 0.20	2.781	0.006
Central region	0.45 ± 0.18	0.53 ± 0.16	2.441	0.016
Top region	0.39 ± 0.21	0.45 ± 0.16	1.461	0.147
Temporal region	0.39 ± 0.17	0.62 ± 0.13	7.127	< 0.001
Occipital region	0.28 ± 0.13	0.34 ± 0.19	1.827	0.070

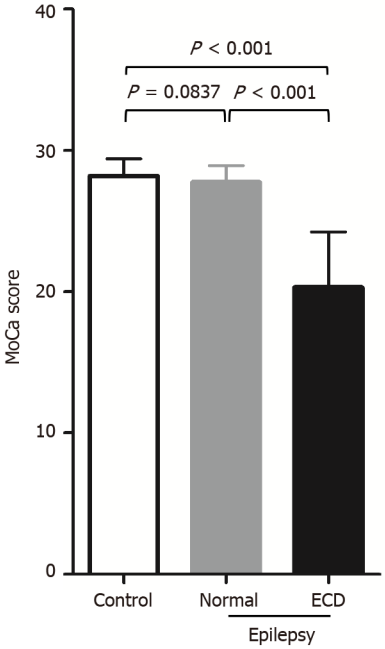
ECD: Epilepsy patients with cognitive dysfunction; ECG: Electrocardiogram.

Ratio of EEG slow wave/fast wave frequency in epilepsy patients

Patients in the normal and ECD groups showed different EEG slow wave/fast wave frequency ratios (EEG value). Patients in the normal group recorded lower EEGs values in the frontal, central, top, temporal, and occipital regions than patients in the ECD group. However, significant differences in EEG values were observed only in the frontal, central, and temporal regions ($P < 0.05$, Table 2).

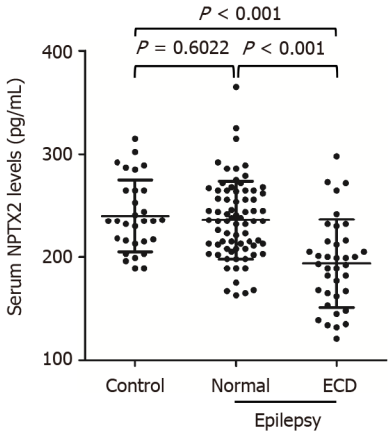
Relationship between NPTX2 serum levels and EEG values

The correlation analysis showed that NPTX2 serum levels in the group were not correlated with EEG values in the frontal or central region ($P > 0.05$). However, NPTX2 serum levels in the group were negatively correlated with the EEG values



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Figure 1 Mini-mental state examination score of cognitive function among the study participants. Control: Healthy volunteers (*n* = 30); Normal: Epilepsy patients with normal cognitive function (*n* = 74); epilepsy patients with cognitive dysfunction (*n* = 37). ECD: Epilepsy patients with cognitive dysfunction; MoCa: Montreal Cognitive Assessment; MMSE: Mini-mental state examination.



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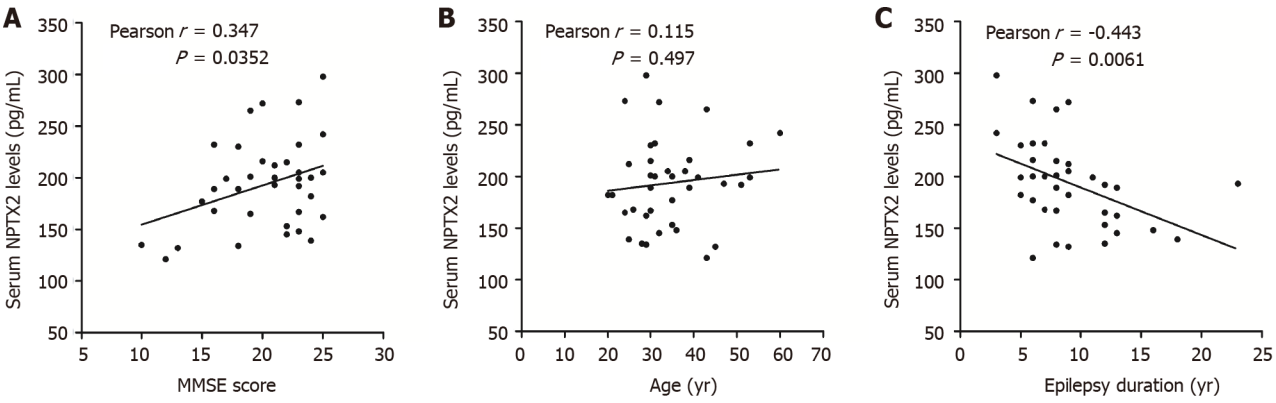
Figure 2 Serum levels of neuronal pentraxin 2 among study participants. Control: Healthy volunteers (*n* = 30); Normal: Epilepsy patients with normal cognitive function (*n* = 74); epilepsy patients with cognitive dysfunction (*n* = 37). ECD: Epilepsy patients with cognitive dysfunction; NPTX2: Neuronal pentraxin 2.

in the temporal region ($P < 0.05$, Figure 5).

Predictive analysis of NPTX2 serum levels and EEG values of the temporal region in cognitive dysfunction

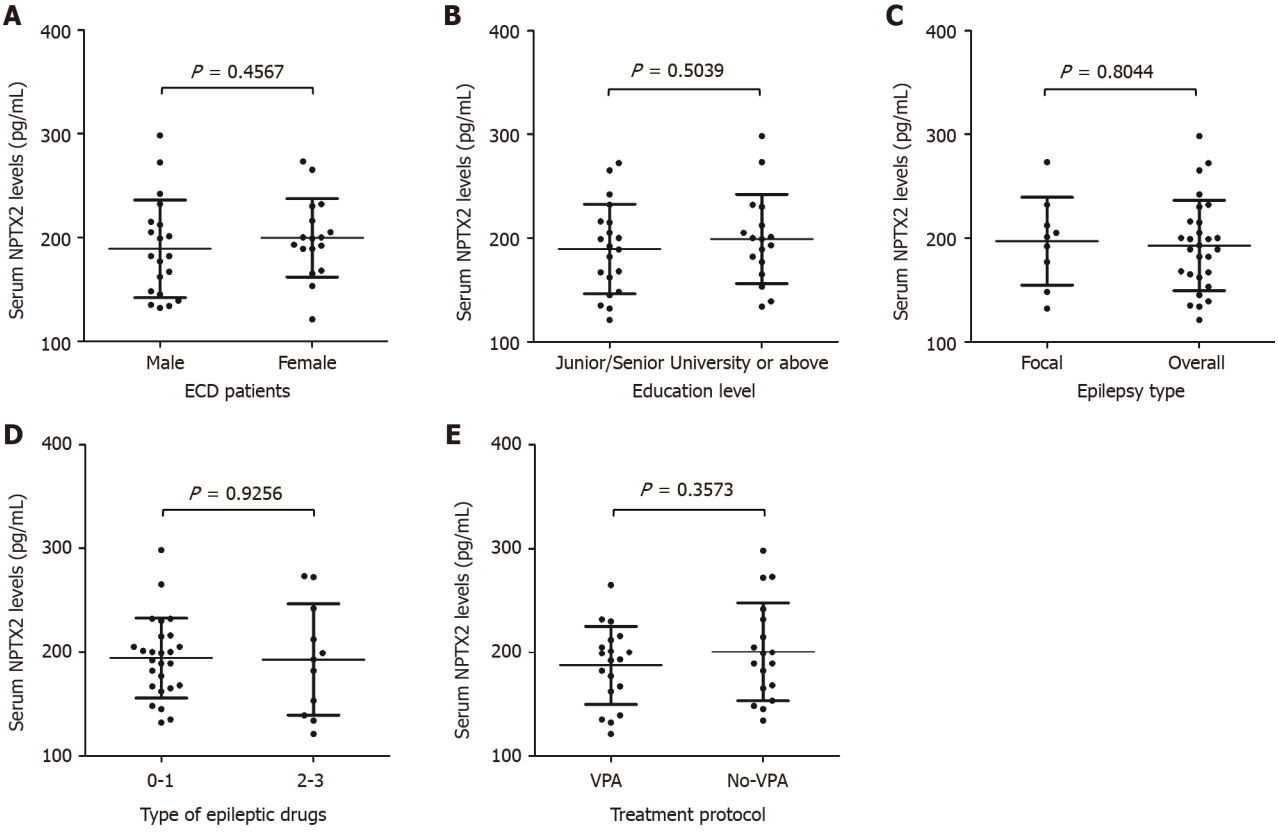
The AUC value of NPTX2 for diagnosing cognitive impairment in epilepsy patients is 0.777, and the 95%confidence interval (95%CI) is 0.679-0.876 (Figure 6). When the cutoff NPTX2 serum level for distinguishing cognitive function in patients with epilepsy was 206.50 pg/mL, the sensitivity and the specificity was 91.89% and 85.14%, respectively (Figure 6).

Moreover, the AUC value of electrocardiogram (ECG) for diagnosing cognitive impairment in epilepsy patients is 0.815, and the 95%CI is 0.739–0.892 (Figure 6). When the cutoff EEG value for distinguishing cognitive function in patients with epilepsy in the temporal region was set at 0.455, the sensitivity and the specificity was 91.89% and 68.92%, respectively (Figure 6).



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Figure 3 Correlation between Neuronal pentraxin 2 levels and Mini-mental state examination score, age and epilepsy duration. A to C: Correlation between serum levels of NPTX2 and MMSE score in (A), age (B), and epilepsy duration (C) in epilepsy patients with cognitive dysfunction. NPTX2: Neuronal pentraxin 2; MMSE: Mini-mental state examination.

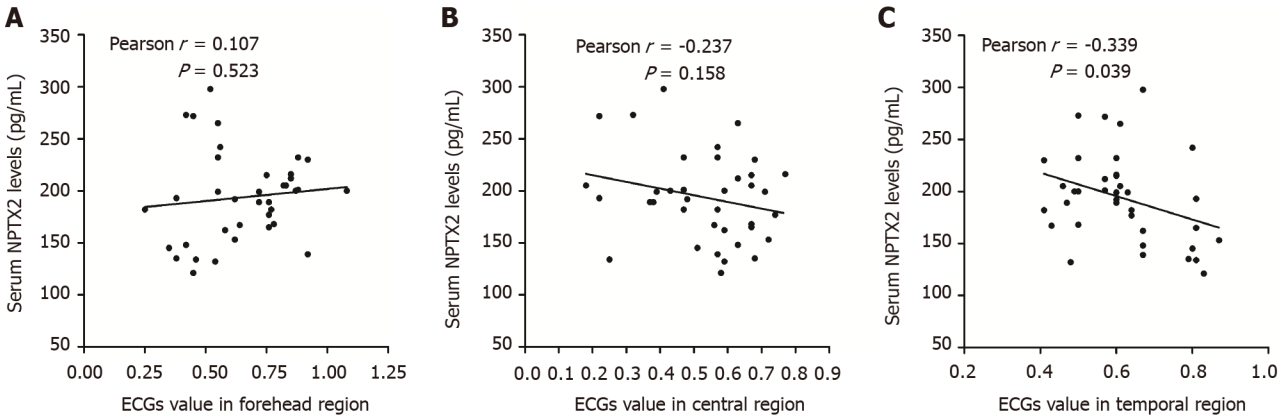


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Figure 4 Comparison between neuronal pentraxin 2 serum levels and different variables in patients with epilepsy and cognitive dysfunction. A to E: Gender(A), education level (B), epilepsy type (C), epilepsy drug types (D), and treatment protocol (E). ECD: Epilepsy patients with cognitive dysfunction; NPTX2: Neuronal pentraxin 2; VPA: Valproate.

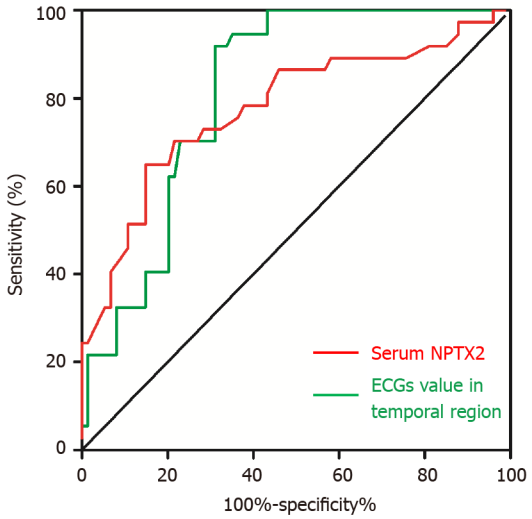
DISCUSSION

Epilepsy is a disease that damages the nervous system, causing damage to the patient's nervous system and subsequently leading to cognitive impairment[17,18]. Epilepsy patients with cognitive impairment are affected in various aspects of their lives. However, it can be confirmed that if diagnosed in the early stages of neu-rological damage, existing medicine has the ability to mitigate cognitive impairment caused by epilepsy. Due to the lack of biomarkers for diagnosing neurological damage in epilepsy patients, it is very difficult to diagnose early neurological damage in epilepsy patients, which also leads to varying degrees of cognitive impairment in epilepsy patients as adults. Therefore, there is a need to develop novel biomarkers for the early detection of cognitive impairment in epilepsy patients.



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Figure 5 Relationship between NPTX2 levels and ECG values in different regions. Correlation between NPTX2 serum levels and EEG values in the frontal (A), central (B), and temporal (C) regions of patients with epilepsy and cognitive dysfunction. ECG: Electrocardiogram; NPTX2: Neuronal pentraxin 2.



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Figure 6 Receiver operating characteristic curve for predicting serum level values and electroencephalogram values in temporal region in patients with epilepsy and cognitive dysfunction. ECG: Electrocardiogram; NPTX2: Neuronal pentraxin 2.

In this study, we first found that the serum NPTX2 in epilepsy were strongly higher than that in healthy people, and is related to the cognitive function score of epilepsy patients. However, previous studies have shown that NPTX2 is associated with neurological damage, such as significantly accelerating the onset time of Parkinson's mice by upregulating NPTX2 blood levels, and NPTX2 has been identified as associated with neurological damage in Parkinson's patients. In addition, previous studies have also found that the level of NPTX2 in the hippocampus of mice decreases due to cognitive decline caused by neuropathic pain, and it is related to cognitive function in mice after cerebral ischemia[19].

In 1995, NPTX2, a secreted protein, was first discovered[20]. Subsequently, research on NPTX2 was reported, and its main function was mainly studied in synapses, indicating that NPTX2 plays an important role in the nervous system[21, 22]. This function makes NPTX2 associated with the occurrence and development of many neurological diseases, such as stroke, Huntington's disease, and Amyotropic lateral sclerosis[23]. The development and damage of the nervous system are closely related to cognitive function, especially in the hippocampus, and has been reported to have significant expression levels in the cerebrospinal fluid of Alzheimer's disease patients, and it is related to the patient's cognitive function score[24]. In this study, we not only found that the levels of serum NPTX2 in ECD group were lowest, but also found that NPTX2 levels was strongly related to the the patient's cognitive function score. Therefore, these data indicate that NPTX2 is associated with nerve injury and cognitive impairment caused by nerve injury, making it a potential biomarker for diagnosing cognitive impairment in epilepsy patients.

EEG is widely used for diagnosis, identification, prognosis evaluation, and treatment efficacy assessment for neurological diseases, including epilepsy[25]. Quantitative EEG transforms the brain wave signals from the time domain in the ordinary EEG into the frequency domain[26]. Due to the inability to effectively control the onset time and pattern of epilepsy patients, it is very difficult for us to detect the EEG during the seizure period of epilepsy patients. Therefore, researchers usually study the EEG during the interval between seizures[27]. Therefore, we selected EEG in the

background of the interseizure period. This study found lower EEG values in the frontal, central, top, temporal, and occipital regions of patients with epilepsy and normal cognitive function than in those with epilepsy and cognitive dysfunction. Importantly, this study also found that NPTX2 serum levels were negatively correlated with EEG values in the temporal region of patients with epilepsy and cognitive dysfunction. These findings suggest that NPTX2 serum levels and temporal region's EEG values is related to cognitive impairment in epilepsy patients.

This study has several limitations. First, this study was conducted in a single center, and had a low sample size. Second, we did not monitor NPTX2 serum levels dynamically. Third, several factors that could affect NPTX2 serum levels—such as smoking, alcohol use, and drug use history—were not considered. Finally, our patient follow-up period was short.

CONCLUSION

In this study, we found that NPTX2 levels in epilepsy patients were lower than those in the healthy population and were associated with cognitive function scores, seizure duration, and ECG values in epilepsy patients. All in all, these results indicate that serum NPTX2 levels are potential biomarkers for diagnosing cognitive dysfunction in epilepsy patients.

ARTICLE HIGHLIGHTS

Research background

Cognitive dysfunction is a common complication in epileptic patients, but there is a lack of effective diagnostic biomarkers. This study investigated the relationship between serum levels of neuronal pentraxin 2 (NPTX2), an important molecule involved in neurotransmission and synaptic plasticity, and cognitive dysfunction in epilepsy patients. The study also explored the association between electroencephalogram (EEG) slow wave/fast wave frequency ratio and cognitive impairment. The aim was to determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in epilepsy patients, addressing the need for reliable diagnostic tools in this population.

Research motivation

The high incidence of cognitive dysfunction in epileptic patients highlights the need for effective diagnostic biomarkers. Currently, there is a lack of reliable tools to identify cognitive impairment in this population. This study aimed to investigate the correlation between serum NPTX2 levels and EEG slow wave/fast wave frequency ratios with cognitive dysfunction in epilepsy patients. By exploring these potential biomarkers, the study aimed to contribute to the development of a diagnostic tool for identifying cognitive impairment in epilepsy patients, facilitating early intervention and improved patient care.

Research objectives

The main objectives of this study were to investigate the relationship between serum levels of NPTX2 and EEG with cognitive dysfunction in epilepsy patients. The study aimed to determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in patients with epilepsy. Additionally, the study aimed to assess the correlation between serum NPTX2 levels, EEG patterns, and cognitive function using the mini-mental state examination (MMSE) scale. The ultimate goal was to contribute to the development of effective diagnostic tools for identifying cognitive impairment in epilepsy patients.

Research methods

The study enrolled three groups of participants: Normal group, 74 epilepsy patients without cognitive dysfunction; epilepsy patients with cognitive dysfunction group, 37 epilepsy patients with cognitive dysfunction; Control group, 30 healthy individuals. Cognitive function was evaluated using the MMSE scale. Serum levels of NPTX2 were measured using an enzyme-linked immunosorbent kit, and EEG recordings were used to calculate the slow wave/fast wave frequency ratio in different EEG regions. Statistical analyses were performed to compare variables among the groups and assess correlations between biomarkers and cognitive function. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of serum NPTX2 and EEG patterns for cognitive dysfunction in epilepsy patients.

Research results

The study found no significant differences in age, gender, or education level among the three groups. There were also no significant differences in epilepsy-related factors between the normal group and the cognitive dysfunction group. Serum levels of NPTX2 were significantly higher in the normal group compared to the cognitive dysfunction group, while the control group showed no significant difference from the normal group. The cognitive dysfunction group had the lowest MMSE scores. The EEG slow wave/fast wave frequency ratio values were significantly higher in the cognitive dysfunction group compared to the normal group in various EEG regions. In epilepsy patients with cognitive dysfunction, NPTX2 levels correlated positively with the MMSE score and negatively with epilepsy duration and the EEG slow wave/fast wave frequency ratio value in the temporal region. ROC curve analysis demonstrated that serum NPTX2

level and EEG patterns had diagnostic potential for evaluating cognitive dysfunction in epilepsy patients.

Research conclusions

The study concluded that serum NPTX2 levels are associated with cognitive dysfunction and the EEG slow wave/fast wave frequency ratio in epilepsy patients. Serum NPTX2 shows potential as a diagnostic biomarker for cognitive impairment in epilepsy. The study found no significant differences in demographic and epilepsy-related factors between the normal and cognitive dysfunction groups. However, serum NPTX2 levels were significantly higher in the normal group compared to the cognitive dysfunction group. The EEG slow wave/fast wave frequency ratios were also higher in the cognitive dysfunction group. These findings suggest that serum NPTX2 and EEG patterns may serve as valuable indicators for diagnosing cognitive impairment in epilepsy patients.

Research perspectives

The findings of this study highlight the potential of serum NPTX2 as a diagnostic biomarker for cognitive impairment in epilepsy patients. Further research is needed to validate and expand upon these results. Future studies could explore the underlying mechanisms linking NPTX2 levels and cognitive dysfunction, investigating the role of NPTX2 in neurotransmission and synaptic plasticity. Additionally, larger sample sizes and longitudinal studies could provide more robust evidence regarding the relationship between serum NPTX2, EEG patterns, and cognitive dysfunction. Ultimately, establishing reliable biomarkers could aid in early detection and intervention for cognitive impairments in epilepsy, improving patient outcomes and quality of life.

FOOTNOTES

Author contributions: Huang X, Lin Y, and Wang F were responsible for the study's conception and design; Xu M and Chen Y provided administrative support; Huang X and Lin Y provided the study materials and patients; Xu M and Lin Y conducted data collection; Chen Y and Wang F conducted data analysis and interpretation; all authors contributed to the manuscript writing process and granted final approval for the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia

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Abstract

BACKGROUND

The gut microbiome interacts with the central nervous system through the gut-brain axis, and this interaction involves neuronal, endocrine, and immune mechanisms, among others, which allow the microbiota to influence and respond to a variety of behavioral and mental conditions.

AIM

To explore the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia.

METHODS

A total of 498 untreated patients with schizophrenia admitted to our hospital from July 2020 to July 2022 were selected as the case group, while 498 healthy volunteers who underwent physical examinations at our hospital during the same period were selected as a control group. Fluorescence *in situ* hybridization was employed to determine the total number of bacteria in the feces of the two groups. The cognitive function test package was used to assess the score of cognitive function in each dimension. Then, the relationship between gut microbiota and cognitive function was analyzed.

RESULTS

There were statistically significant differences in the relative abundance of gut microbiota at both phylum and class levels between the case group and the control group. In addition, the scores of cognitive function, such as attention/alertness and learning ability, were significantly lower in the case group than in the control group (all $P < 0.05$). The cognitive function was positively correlated with Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudo-

monadota, and Saccharibacteria, while negatively correlated with Bacillota, Tenericutes, and Verrucomicrobia at the phylum level. While at the class level, the cognitive function was positively correlated with Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, while negatively correlated with Bacilli, Clostridia, Coriobacteriia, and Verrucomicrobiae.

CONCLUSION

There is a relationship between the metabolic results of gut microbiota and cognitive function in patients with schizophrenia. When imbalances occur in the gut microbiota of patients, it leads to more severe cognitive impairment.

Key Words: Schizophrenia; Cognitive function; Gut microbiota; Metabolic imbalance; Bacteria

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Core Tip: The highlights of this study are as follows. First, individuals with schizophrenia have imbalanced intestinal microbiota compared to healthy individuals. Second, patients with schizophrenia exhibit cognitive impairments in various areas such as attention, memory, social cognition, and executive function. Additionally, specific microbial groups such as Actinomycetes, Bacteroides, and Proteobacteria have shown a positive correlation with cognitive function in patients with schizophrenia. Furthermore, there is a close relationship between metabolic imbalance of intestinal flora and cognitive impairment in individuals with schizophrenia. Lastly, further clinical trials are necessary to gather more data and insights for the development of effective treatments for schizophrenia.

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INTRODUCTION

Schizophrenia is a severe mental disorder with unknown etiology. Most of the patients are young and middle-aged. Frequently, the patients may encounter various obstacles in thinking, perception, emotion, and behavior, leading to a lack of coordination between mental activities and the surroundings[1]. Patients with schizophrenia exhibit characteristics such as a high disability rate, substantial burden, and an increased tendency of suicide. This disorder also causes hallucinations, delusions, language, and behavior abnormalities, with a long course and heterogeneous clinical manifestations. Schizophrenia has an impact on the physical and mental health, as well as social quality of life for patients, resulting in economic pressure and social burden. With the continuous advancement of biological technology, the understanding of schizophrenia is gradually deepening[2,3]. As one of the primary symptoms of schizophrenia, cognitive dysfunction includes two aspects, mental cognition and social cognition. Generally, it manifests before other psychotic symptoms of schizophrenia and persists throughout the course of the disease[4]. In recent years, there has been an increasing focus on the cognitive impairment of patients. Cognitive impairment can impede patients' social and occupational rehabilitation, and assessing cognitive function can predict the disease progression and treatment response[5]. Gut microbiota constitutes a complex and vast ecosystem. Scholars have proposed that gut microbiota can regulate the immune and inflammatory responses within the human body and influence neural development. However, the understanding of the relationship between gut microbiota and schizophrenia is still limited[6,7].

In this study, cognitive function and gut microbiota were examined to explore the potential correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia.

MATERIALS AND METHODS

Materials

A total of 498 patients with schizophrenia admitted to The First Affiliated Hospital of Zhengzhou University from July 2020 to July 2021 were selected as the case group, and 498 healthy volunteers who underwent physical examination at the same hospital were randomly chosen as the control group.

Inclusion criteria were: patients who met the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[8], patients with no abnormality in routine blood tests, and patients who were 18-years-old to 50-years-old.

Exclusion criteria were: patients with diabetes, thyroid disease, hypertension, heart disease, or other diseases that may affect the stability of gut microbiota; patients who suffered from diarrhea in the past 3 mo; or patients who were pregnant or lactating.

Determination of bacterial counts

The bacterial counts in patients were determined using fluorescence *in situ* hybridization. We utilized fluorescent tags as a substitute for isotope labeling. First, biotin labeling was carried out, followed by DNA probe hybridization. Next, fluorescein avidin was used to bind with the probe hybridization to the target DNA on the chromosomes to form a hybrid. Qualitative and quantitative analyses were then performed after detecting the fluorescence under a microscope.

Cognitive function scores

The first step was to determine whether the patient was conscious. Generally, the Glasgow scale was employed to assess the degree of consciousness disturbance. If the patient was conscious, the Short Form Mental State Examination was used to screen for cognitive dysfunction. Based on the results, the presence of cognitive impairment could be identified, and further assessment of cognitive function was conducted accordingly.

Statistical processing

SPSS21.0 software was used for the data analyses. The independent *t*-test was used for comparisons between the two groups. For multivariate regression analysis, the multiple linear regression model was employed when the dependent variable was continuous, whereas the logistic regression model was used when the dependent variable was dichotomous. $P < 0.05$ was considered statistically significant.

RESULTS

Distribution of gut microbiota at the phylum level in the two groups

As shown in Table 1, the case group exhibited a significantly higher relative abundance of Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudomonadota, and lower abundance of Bacillota, Tenericutes, and Verrucomicrobia when compared with the control group ($P < 0.05$).

Distribution of gut microbiota at the class level in the two groups

As shown in Table 2, compared with the control group, the case group exhibited a significantly higher relative abundance of Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, and lower relative abundance of Bacilli, Clostridia, Coriobacteriia, and Verrucomicrobiae ($P < 0.05$).

Comparison of cognitive scores between the two groups

As shown in Table 3, the scores of attention or alertness, learning, memory, fine motors, social cognition, executive function, conversion, inhibition, planning, working memory, category fluency, information processing, and total cognitive score were all significantly lower in the case group than in the control group ($P < 0.05$).

Correlation analysis between cognitive function and gut microbiota at the phylum level

As shown in Table 4, cognitive function was positively correlated with Actinomycetota ($r = 6.591$, $P = 0.001$), Bacteroidota ($r = 5.625$, $P = 0.016$), Euryarchaeota ($r = 6.281$, $P = 0.183$), Fusobacteria ($r = 2.190$, $P = 0.026$), Pseudomonadota ($r = 6.364$, $P = 0.018$), and Saccharibacteria ($r = 5.196$, $P = 0.037$), while negatively correlated with Bacillota ($r = -0.976$, $P = 0.281$), Tenericutes ($r = -0.623$, $P = 0.001$), and Verrucomicrobia ($r = -0.191$, $P = 0.006$).

Correlation analysis of between cognitive function and gut microbiota at the class level

As shown in Table 5, cognitive function was positively correlated with Class Actinobacteria ($r = 3.257$, $P = 0.001$), Bacteroidia ($r = 6.294$, $P = 0.001$), Betaproteobacteria ($r = 6.281$, $P = 0.016$), Proteobacteria ($r = 6.270$, $P = 0.008$), Blastomycetes ($r = 5.671$, $P = 0.006$), and Gammaproteobacteria ($r = 4.195$, $P = 0.005$), while negatively correlated with Bacilli ($r = -0.981$, $P = 0.001$), Clostridia ($r = -0.124$, $P = 0.015$), Coriobacteriia ($r = -0.293$, $P = 0.019$), and Verrucomicrobiae ($r = -0.549$, $P = 0.010$).

DISCUSSION

Schizophrenia is a chronic and severe mental disorder characterized by disturbances in an individual's sensory, emotional, and behavioral functions[9]. Patients with schizophrenia have difficulties distinguishing between reality and the imaginary. They may exhibit slow reactions, and show a phenomenon of behavioral withdrawal, significantly affecting their ability to engage in normal social behavior. In medical terms, schizophrenia is classified as a disorder rather than a disease. This disorder often typically occurs during the young or prime stages of life. It encompasses disturbances in the body, mind, emotions, and behaviors, but the patients do not have a coma or mentally retarded imagination[10,11]. Some studies have found that genetic factors, brain structure, and environment factors contribute

Table 1 Relative abundance of gut microbiota at the phylum level in the two groups

Name of bacteria	Case group, *n* = 498	Control group, *n* = 498	*T* value	*P* value
Actinomycetota	2.95 ± 5.62	2.18 ± 3.60	2.575	0.01
Bacteroidota	34.27 ± 19.53	26.84 ± 16.07	6.556	0.001
Euryarchaeota	0.16 ± 0.57	0.00 ± 0.00	6.264	0.001
Bacillota	48.82 ± 17.96	61.37 ± 14.49	12.14	0.001
Fusobacteria	0.08 ± 0.57	0.02 ± 0.07	2.332	0.019
Pseudomonadota	15.82 ± 20.13	7.68 ± 11.59	7.82	0.001
Saccharibacteria	0.49 ± 0.27	0.01 ± 0.01	39.65	0.001
Tenericutes	0.23 ± 1.14	0.59 ± 1.92	3.598	0.001
Verrucomicrobia	0.57 ± 1.94	1.62 ± 5.19	4.229	0.001
Actinomycetota	2.95 ± 5.62	2.18 ± 3.60	2.575	0.01

Data are presented as mean ± SD.

Table 2 Relative abundance of gut microbiota at the class level in the two groups

Name of bacteria	Case group, *n* = 498	Control group, *n* = 498	*T* value	*P* value
Class Actinobacteria	2.81 ± 5.64	1.56 ± 2.81	4.427	0.001
Bacilli	2.01 ± 4.28	2.67 ± 5.60	2.090	0.036
Bacteroidia	31.28 ± 19.67	26.68 ± 16.18	4.030	0.001
Betaproteobacteria	1.50 ± 3.29	0.39 ± 0.52	7.437	0.001
Clostridia	45.92 ± 18.62	58.18 ± 13.92	11.770	0.001
Coriobacteriia	0.21 ± 0.49	0.58 ± 1.29	5.984	0.001
Proteobacteria	0.29 ± 0.39	0.15 ± 0.24	6.822	0.001
Blastomycetes	0.96 ± 1.19	0.67 ± 1.20	3.829	0.01
Gammaproteobacteria	13.84 ± 19.67	6.92 ± 11.37	6.797	0.001
Verrucomicrobiae	0.58 ± 1.69	1.82 ± 5.86	4.537	0.001

Data are presented as mean ± SD.

significantly to the development of this disorder. Therefore, comprehensive medical and psychological treatments are necessary to address the multifaceted nature of the condition.

Cognitive impairment is commonly observed in patients with schizophrenia, impacting various aspects such as information integration, memory, and attention. Symptoms of cognitive dysfunction are prominently manifested through memory decline in the general population[12,13]. In addition to memory decline, schizophrenia can result in impairments in executive function, visuospatial ability, comprehension, and numeracy. People's general cognition and social cognition are also closely associated with age. As the aging population continues to grow, the incidence of cognitive dysfunction is increasing[14,15]. A large number of clinical studies have demonstrated a certain correlation between schizophrenia and cognitive function. Effective interventions targeting overall cognition, emotions, and society aspects have shown promising results. In this study, patients with schizophrenia exhibited considerable declines in various cognitive aspects, including learning, memory, fine motor skills, social cognition, working memory, category fluency, information processing, and kinetic energy, when compared to healthy individuals. These results suggest association between cognitive function and schizophrenia, which is similar to the results of the above research.

Schizophrenia has profoundly impacted numerous families. Consequently, there is a paramount need to pursue effective treatment options and improve the patient prognosis[16]. Gut microbiota is a central regulator of metabolism in the human body and has been found to be associated with various mental diseases[17,18]. In modern society, there is a growing awareness of the diversity, complexity, and dynamics of gut microbiota. Differences in the structure and diversity of gut microbiota have been observed in patients with schizophrenia, with the control of the disorder having a great impact on the distribution of gut microbiota structure[19,20]. Some scholars have noted that alterations in the gut microbial community can affect the cytokine levels in the body, subsequently impacting the brain function and behaviors,

Table 3 Comparative analysis of cognitive scores between the two groups

Cognitive domain	Case group, *n* = 498	Control group, *n* = 498	*T* value	*P* value
Attention/alertness	40.27 ± 6.29	51.98 ± 9.92	22.250	0.001
Learning	36.27 ± 10.01	50.69 ± 10.08	22.650	0.001
Memory	40.31 ± 11.26	54.27 ± 7.19	23.320	0.001
Fine motors	37.29 ± 13.27	59.06 ± 7.91	31.450	0.001
Social cognition	41.09 ± 11.08	54.26 ± 10.87	18.930	0.001
Executive function	40.18 ± 7.04	52.37 ± 5.09	31.310	0.001
Conversion	41.06 ± 7.21	49.57 ± 7.61	18.120	0.001
Inhibition	38.62 ± 9.51	54.63 ± 9.67	26.340	0.001
Planning	42.14 ± 13.01	52.67 ± 10.17	14.230	0.001
Working memory	42.09 ± 13.02	53.19 ± 9.06	15.620	0.001
Category fluency	39.86 ± 10.05	53.18 ± 9.07	21.960	0.001
Information processing	33.43 ± 9.14	48.45 ± 7.39	28.520	0.001
Total score	40.64 ± 7.17	51.14 ± 5.29	26.300	0.001

Data are presented as mean ± SD of points.

Table 4 Correlation analysis between the total cognitive score and gut microbiota at the phylum level

Name of bacteria	Total cognitive score	
	R value	*P* value
Actinomycetota	6.591	0.001
Bacteroidota	5.625	0.016
Euryarchaeota	6.281	0.183
Bacillota	0.976	0.281
Fusobacteria	2.190	0.026
Pseudomonadota	6.364	0.018
Saccharibacteria	5.196	0.037
Tenericutes	0.623	0.001
Verrucomicrobia	0.191	0.006

and greatly affecting the prognosis of patients. In this study, we found that the relative abundance of gut microbiota in patients with schizophrenia differed significantly from that in healthy individuals, indicating an imbalance in the gut microbiota in patients with schizophrenia, which is consistent with the previous results. This article examined gut microbiota at a phylum level (Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudomonadota, *etc*) and a class level (Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, *etc*). The results suggest that there is a certain correlation between gut microbiota and schizophrenia.

In this study, a correlation was identified between cognitive impairment and metabolic imbalance of gut microbiota. However, it is essential to acknowledge that the small sample size in this study may introduce some bias in the data. In the future, clinical trials with larger sample size should be conducted to provide more reliable data to guide the clinical treatment for patients with schizophrenia.

CONCLUSION

To summarize, this study revealed the presence of gut microbiota imbalance in schizophrenia patients and found the correlation between cognitive impairment and metabolic imbalance of gut microbiota in these patients. of intestinal flora, providing insights into the link between changes in gut microbiota and cognitive function, as well as the pathogenesis of schizophrenia. This research presents a novel approach that may pave the way for future treatments targeting schizo-

Table 5 Correlation analysis between the total cognitive score and gut microbiota at the class level

Name of bacteria	Total cognitive score	
	R value	*P* value
Actinobacteria	3.257	0.001
Bacilli	0.981	0.001
Bacteroidia	6.294	0.001
Betaproteobacteria	6.281	0.016
Clostridia	0.124	0.015
Coriobacteriia	0.293	0.019
Proteobacteria	6.270	0.008
Blastomycetes	5.671	0.006
Gammaproteobacteria	4.195	0.005
Verrucomicrobiae	0.549	0.010

phrenia.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a severe mental disorder characterized by impaired thinking, perception, emotion, and behavior. It affects the physical and mental health of the patients, leading to a high disability rate, burden, and suicide tendency. Cognitive dysfunction is a primary symptom of schizophrenia and includes mental cognition and social cognition. It can significantly impact the overall functioning and quality of life of individuals with schizophrenia. In recent years, there has been increasing recognition of the importance of cognitive function in schizophrenia. Cognitive impairment can not only predict the progression of the disease but also affect the treatment response and functional outcomes. Therefore, understanding the factors that contribute to cognitive impairment in schizophrenia is crucial for improving patient outcomes. Gut microbiota, a complex ecosystem of microorganisms residing in the gastrointestinal tract, has been found to play a role in regulating immune and inflammatory responses, as well as influencing neural development. Emerging evidence has suggested a potential connection between gut microbiota and psychiatric disorders, including schizophrenia. However, the specific relationship between gut microbiota and cognitive impairment in schizophrenia patients remains limited and requires further exploration.

Research motivation

Recent research has suggested a potential link between gut microbiota and psychiatric disorders, including schizophrenia. However, the specific relationship between gut microbiota and cognitive impairment in schizophrenia remains poorly understood. This knowledge gap necessitates further investigation to explore the potential role of gut microbiota in the cognitive dysfunction observed in schizophrenia.

The motivation behind this study is to bridge this gap by investigating the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia. By examining the composition of gut microbiota and evaluating cognitive function in a large sample of untreated schizophrenia patients, we aimed to shed light on the potential mechanisms underlying cognitive dysfunction in this population.

The findings of this study provide significant clinical implications and contribute to the development of novel therapeutic strategies targeting the gut microbiota to improve cognitive outcomes of patients with schizophrenia. Ultimately, this research aims to enhance the understanding of the complex interplay between gut microbiota and cognitive impairment in schizophrenia, leading to improved diagnosis, treatment, and overall management of this mental disorder.

Research objectives

The objective of this research was to explore the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia. The study compared the composition and abundance of gut microbiota in untreated schizophrenia patients and healthy controls, evaluated cognitive function using a consensus version of the cognitive function test package, and examined the relationship between specific microbial groups and cognitive function.

Research methods

The research employed a case-control study design. A total of 498 untreated schizophrenia patients admitted to the

hospital from July 2020 to July 2022 were selected as the case group, while 498 healthy volunteers who underwent physical examinations at the same hospital during the same period served as the control group. The composition and abundance of gut microbiota were assessed using fluorescence *in situ* hybridization to determine the total number of bacteria in fecal samples from both groups. Cognitive function was evaluated using a cognitive function test package consensus version, which assesses various dimensions of cognitive function. Statistical analysis was performed to compare the relative abundance of actinomycetes and other microbial groups between the case and control groups, as well as to examine the relationship between specific gut microbiota and cognitive function. The statistical significance level was set at $P < 0.05$.

Research results

The research findings revealed the correlation between gut microbiota and cognitive function in patients with schizophrenia. There was a statistically significant difference in the relative abundance of Actinomycetota between the case group and the control group, indicating an imbalance in the gut microbiota of schizophrenia patients. Moreover, compared to the control group, the schizophrenia patients demonstrated statistically significant differences in scores related to attention/alertness, and learning ability, suggesting impaired cognitive function in these areas. Furthermore, specific microbial groups showed correlations with cognitive function: Actinomycetota, Bacteroidota, Fusobacteria, and Proteobacteria were found to be positively associated with cognitive function, while the Coriobacteriia showed a negative correlation. These findings provide evidence of the influence of gut microbiota on cognitive impairment in schizophrenia patients and underscore the importance of addressing gut microbiota imbalance as a potential therapeutic target for improving cognitive outcomes in this population.

Research conclusions

In conclusion, this research confirmed a relationship between gut microbiota metabolic imbalance and cognitive function in patients with schizophrenia. The study findings indicate that when there is an imbalance in the composition of gut microbiota, the cognitive function of schizophrenia patients is more severely affected. The relative abundance of Actinomycetota was found to significantly differ between the case group and the control group, suggesting an imbalance in gut microbiota in schizophrenia patients. Additionally, specific microbial groups, including Actinomycetota, Bacteroidota, Fusobacteria, and Proteobacteria, were positively correlated with cognitive function, while the Coriobacteriia showed a negative correlation. These results emphasize the importance of addressing gut microbiota imbalances as a potential target for improving cognitive impairment in schizophrenia patients. Further research and interventions focused on modulating gut microbial composition and promoting gut health may lead to improved cognitive outcomes in this population.

Research perspectives

In future research, it is recommended to conduct longitudinal studies to observe changes in gut microbiota and cognitive function over time in schizophrenia patients, as well as intervention studies to investigate the effects of modulating gut microbiota on cognitive outcomes. Mechanistic studies can provide insights into the underlying mechanisms of the gut-brain axis in schizophrenia. The identification of specific gut microbiota markers as diagnostic or prognostic biomarkers for cognitive impairment, exploring individual differences, and developing personalized therapeutic strategies are also important areas for further investigation. By pursuing these research perspectives, we can advance our understanding of the role of gut microbiota in schizophrenia-related cognitive impairment and potentially develop targeted interventions to improve cognitive outcomes in this population.

FOOTNOTES

Author contributions: Ma J and Song XQ designed the study; Ma J wrote the manuscript; Ma J and Song XQ collected and analyzed the data; Ma J and Song XQ revised and reviewed the manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Sleep disturbances are associated with anxiety, depression, and decreased quality of life in patients with coronary heart disease

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Abstract

BACKGROUND

Studies have shown that sleep disorders are closely related to anxiety and depression, and the quality of life (QoL) of patients with sleep disorders is generally poor.

AIM

To examine the occurrence of sleep disorders in people with coronary heart disease (CHD) and their relationships with QoL, depression, and anxiety.

METHODS

As per the sleep condition, 240 CHD individuals were separated into two groups: non-sleep disorder group (n = 128) and sleep disorder group (n = 112). The self-rating anxiety scale (SAS), self-rating depression scale (SDS), and World Health Organization criteria for the Quality of Life Brief scale (WHOQOL-BREF) scores of the two groups were compared. Logistic regression method was used to analyze the independent risk factors of CHD patients with sleep disorders. Multivariate logistic regression analysis was employed to develop the risk prediction model. The association among the Pittsburgh Sleep Quality Index, SAS, and SDS was examined using Spearman's correlation analysis.

RESULTS

The incidence of sleep disorder was 46.67% in 240 patients. The scores of SAS and SDS in the sleep disorder group were higher than those in the non-sleep disorder group, and the WHOQOL-BREF scores were lower than those in the non-sleep disorder group ($P < 0.05$). The risk prediction model of sleep disturbances in CHD patients was constructed using the outcomes of multivariate logistic regression analysis, $P = 1/[1 + e (-2.160 + 0.989 \times (\text{female}) + 0.001 \times (\text{new rural cooperative medical insurance}) + 2.219 \times (\text{anxiety}) + 2.157 \times \text{depression})]$. The results of a Spearman's correlation study revealed that sleep quality was strongly adversely connected with the physiological field, psychological field, and social relation scores in QoL, and was considerably positively correlated with SAS and SDS ($P < 0.05$).

CONCLUSION

A multivariate logistic regression model can better predict the occurrence of sleep disorders in CHD patients. Sleep disorders in CHD patients are significantly correlated with QoL, depression, and anxiety.

Key Words: Coronary heart disease; Sleep disorder; Quality of life; Depression; Anxiety

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Core Tip: Sleep disorder is a common clinical problem, and the correlation between sleep disorder and anxiety and depression has been widely discussed in clinical practice. This study explored the problem of sleep disorder in patients with coronary heart disease (CHD) and its correlation with anxiety, depression, and quality of life (QoL). The results showed that the incidence of sleep disorder is higher in patients with CHD, and is positively correlated with anxiety and depression, and negatively correlated with QoL.

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INTRODUCTION

Coronary heart disease (CHD) can damage people's health and lead to death. Sleep disorders are a prevalent aspect of CHD that can have a negative effect on a patient's quality of life (QoL), cause coronary events, increase disease progression, and influence patients' survival[1,2]. As a result, treating patients' sleep disorders will enable them to have a longer life expectancy. Exploring the influencing factors of sleep disorders is conducive to further research and evaluation of sleep disorders in CHD patients. Patients with CHD are more likely to experience negative feelings, depression, and anxiety as a result of the disease, which affects their QoL. The reason may be that CHD is critical and difficult to treat and may be accompanied by symptoms such as angina pectoris or arrhythmia, and excessive worry may lead to anxiety and depression[3,4]. There is currently little research on the influence of anxiety and depression on the sleep quality of CHD patients, and there are also few studies on the influence of demographic and clinical factors on sleep problems in CHD patients.

Our present research aimed to study and explore the current status of sleep disorders in CHD patients and its correlation with QoL, depression, and anxiety to establish a standard for therapeutic prevention and management of sleep disturbances in individuals with CHD.

MATERIALS AND METHODS

Data sources

Clinical data were gathered from 240 CHD patients (114 females and 126 males) with an age range of 48-79 years (average age = 61.58 ± 6.93) referred to our facility between January 2020 and September 2022. The study inclusion criteria: (1) All patients met the Diagnostic Criteria for Coronary atherosclerotic Heart Disease[5]; (2) the vital signs were stable after treatment; (3) no history of drug abuse; and (4) patients with normal communication ability. Exclusion criteria were: (1) Patients with depression, schizophrenia, or other mental diseases; (2) patients with cognitive impairment; (3) patients with cerebrovascular disease or central nervous system disease; (4) patients with malignant tumor disease; and (5) patients with heart failure. This study was approved by the ethics committee.

Data collection

General data such as sex, age, disease type, smoking, marital status, hypertension, diabetes, family history of CHD, dyslipidemia, education level, working status, and type of medical insurance of all patients were collected.

Observation indexes

(1) The Pittsburgh Sleep Quality Index (PSQI)[6] score of 240 CHD patients was collected. Each of the seven evaluation items on the scale received a score between 0 and 3, for a range of 0 to 21 points. A score > 7 points denotes poor sleep quality and a sleep disorder, whereas a score of 7 points shows good sleep quality and no sleep disorders. The lower the score, the poorer the sleep quality. Then 240 patients with CHD were divided into the sleep disorder group and non-sleep disorder group according to the PSQI score, and the incidence of sleep disorder in 240 patients with CHD was calculated; (2) The self-rating anxiety scale (SAS)[7] and self-rating depression scale (SDS)[7] scores of CHD patients with and without sleep disturbances were collected and compared. There are 20 items in SAS scale; ≥ 50 is classified as anxiety, and the higher the score, the more serious the anxiety. The SDS scale consists of 20 items; ≥ 53 points indicates depression, and the higher the score, the more serious the degree of depression; (3) The World Health Organization criteria for the Quality of Life Brief scale[8] score of CHD patients with and without sleep disturbances were collected and compared. The scale includes four dimensions, namely physiology, psychology, environment, and social relation, and each dimension scores 0-100 points; (4) A comparison of the general data for the sleep disorder group and the non-sleep disorder group was done; (5) To examine independent risk factors of sleep problems in CHD patients, components with statistically significant variations in basic information were considered in the multivariate logistic regression analysis; (6) The logistic regression analysis findings were used to develop the risk prediction model. The area under the curve (AUC), receiver operating characteristic (ROC), and Hosmer-Lemeshow analyses were employed to examine the model's degree of correlation, and the ROC curve was constructed to demonstrate how effectively the model predicts results. The closer the AUC is to 1.0, the higher the prediction efficiency; and (7) The association among PSQI, SAS, and SDS was investigated using Spearman's correlation analysis.

Statistical analyses

Two individuals working independently entered the study data into Excel tables, and SPSS 24.0 statistical software was employed to examine and interpret the data. The experimental data are expressed as the mean ± SD, and the *t*-test was used to compare homogeneous and normally distributed data. Numbers "*n*" and percentages "%" were employed to characterize the counting data, and the χ^2 test was performed to compare groups. For multivariate analyses, a logistic regression model was utilized, and Spearman's correlation analysis was performed for correlation analyses. The threshold for statistical significance was set at $P < 0.05$ for all bilateral tests.

RESULTS

Comparison of the incidence of sleep disorders in CHD patients

Among the 240 patients, 112 CHD patients had PSQI scores > 7 points and had a sleep disorder, with an incidence of 46.67%.

Comparison of QoL, depression, and anxiety scores of CHD individuals with sleep disorder and without sleep disorders

As can be seen in Table 1, the difference between the SDS and SAS scores in both groups was statistically significant ($P < 0.05$; Figure 1).

Comparison of QoL scores of CHD patients in both groups

The sleep disorder group scored lower on the social relation, psychological field, and physiological field compared to the non-sleep disorder group ($P < 0.05$). Environmental field scores between the two groups were not significantly different ($P > 0.05$) (Figure 2, Table 2).

Single-factor analysis of sleep disorders in CHD patients

No significant difference was observed in both groups in terms of disease type, smoking, marital status, hypertension, diabetes, family history of CHD, dyslipidemia, educational level, and working status. In the group of people with sleep disorders, there were more female patients ($P < 0.05$), patients under the age of 60, individuals in new rural cooperative medical systems, and patients with anxiety and depression (Table 3).

Multivariate logistic regression investigation of sleep disorders in individuals with CHD

The parameters with significant differences in the univariate study of sleep quality disorders in CHD patients were subjected to multivariate logistic regression analysis. The sleep disorder of patients was taken as dependent variables, and sex, age, medical insurance type, anxiety and depression were taken as independent variables (Table 4). Multivariate logistic regression analyses showed that females, new rural cooperative medical insurance, depression, and anxiety were independent risk factors for sleep disorders in individuals with CHD ($P < 0.05$; Table 5).

Establishment and calibration of the multivariate logistic regression model

The risk prediction model of sleep disturbances in CHD patients was established using the results of a multivariate logistic regression study, $P = 1/[1 + e (-2.160 + 0.989 \times (\text{female}) + 0.001 \times (\text{new rural cooperative medical insurance}) + 2.219 \times (\text{anxiety}) + 2.157 \times \text{depression})]$, and the Hosmer-Lemeshow test was used, $\chi^2 = 7.284$, $P = 0.506$, indicating a good

Table 1 Comparison of quality of life, depression, and anxiety scores of patients with coronary heart disease with and without sleep disorders

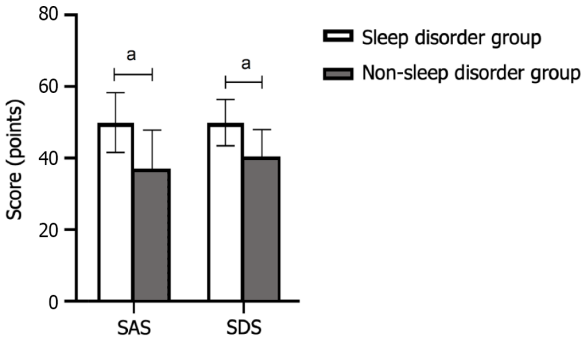
Group	SAS score	SDS score
Sleep disorder group, *n* = 112	49.93 ± 8.37[a]	49.89 ± 6.47[a]
Non-sleep disorder group, *n* = 128	37.02 ± 10.84	40.45 ± 7.53
t value	10.389	10.336
P value	< 0.001	< 0.001

[a]*P* < 0.05 *vs* non-sleep disorder group.
Data (points) are mean ± SD. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

Table 2 Comparison of the quality of life scores of patients with coronary heart disease with and without sleep disorders

Group	Physiological field	Psychological field	Environmental field	Social relation
Sleep disorder group, *n* = 112	35.58 ± 5.75[a]	30.52 ± 4.72[a]	45.98 ± 5.40	42.93 ± 5.45[a]
Non-sleep disorder group, *n* = 128	38.88 ± 5.52	34.92 ± 3.82	46.63 ± 5.74	45.06 ± 4.30
t value	4.524	7.869	0.901	3.334
P value	< 0.001	< 0.001	0.369	0.001

[a]*P* < 0.05 *vs* non-sleep disorder group.
Data (points) are mean ± SD.



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Figure 1 Comparison of both groups' self-rating depression scale and self-rating anxiety scale scores. [a]*P* < 0.05 *vs* non-sleep disorder group. SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

fit between the model and the observed values, as shown in Figure 3.

Prediction efficiency of the logistic regression model

Figure 4 illustrates the outcomes of ROC analysis, which revealed that the model had a good predictive effect ($P < 0.05$). Moreover, the AUC of the risk prediction model for sleep disorders in CHD patients was 0.851 with a 95% confidence interval (CI) of 0.803-0.900.

Correlation between sleep disorders and anxiety, depression, and QoL

As indicated in Table 6, Spearman's correlation analysis revealed that sleep quality exhibited a strong negative association with the physiological field, psychological field, and social relations of QoL, and was positively associated with SAS and SDS ($P < 0.05$; Figures 5 and 6).

DISCUSSION

Sleep disturbances have been linked to an increased risk of CHD and the development of CHD, according to several studies conducted both domestically and internationally[2,9,10]. Disease factors, psychological factors, and environ-

Table 3 Single factor analysis of sleep disorders in patients with coronary heart disease

Factor	Sleep disorder group, *n* = 112	Non-sleep disorder group, *n* = 128	χ^2/t value	*P* value
Sex				
Male	47 (41.69)[a]	79 (61.27)	9.347	0.002
Female	65 (58.04)[a]	49 (38.28)		
Age in yr	62.56 ± 7.18[a]	60.72 ± 6.61	2.070	0.040
≥ 60	56 (50.00)	30 (23.44)		
< 60	56 (50.00)	98 (76.56)		
Disease type				
Stable angina pectoris	57 (50.89)	67 (52.34)	0.050	0.822
Acute coronary syndrome	55 (49.11)	61 (47.66)		
Smoking				
Yes	44 (39.29)	46 (35.94)	0.286	0.593
No	68 (60.71)	82 (64.06)		
Marital status				
Single	6 (5.36)	9 (7.03)	0.286	0.593
Married	106 (94.64)	119 (92.97)		
Hypertension				
Yes	68 (60.71)	74 (57.81)	0.208	0.648
No	44 (47.89)	54 (42.19)		
Diabetes				
Yes	31 (27.68)	29 (22.66)	0.804	0.370
No	81 (72.32)	99 (77.34)		
Family history of CHD				
Yes	25 (22.32)	22 (17.19)	1.000	0.317
No	87 (77.68)	106 (82.81)		
History of dyslipidemia				
Yes	32 (28.57)	39 (30.47)	0.103	0.748
No	80 (71.43)	89 (69.53)		
Education level				
High school and below	54 (48.21)	62 (48.44)	0.001	0.972
College or above	58 (51.79)	66 (51.56)		
Working status				
On-the-job	26 (23.21)	42 (32.81)	3.023	0.221
Waiting for employment	6 (5.36)	8 (6.25)		
Retired	80 (71.43)	78 (60.94)		
Medical insurance type				
Medical insurance for urban workers	45 (40.18)[a]	85 (66.41)	16.551	< 0.001
New rural cooperative medical insurance	67 (59.82)[a]	43 (33.59)		
Anxiety, ≥ 50 points				
Yes	65 (58.04)[a]	14 (10.94)	60.006	< 0.001
No	47 (41.96)[a]	114 (89.06)		
Depression, ≥ 53 points				

Yes	41 (36.16)[a]	7 (5.47)	36.1987	< 0.001
No	71 (63.39)[a]	121 (94.53)		

[a]*P* < 0.05 *vs* non-sleep disorder group.
Data are mean ± SD or *n* (%). CHD: Coronary heart disease.

Table 4 Assignment

Factor	Assignment method
Age in yr	≥ 60 yr = 1, < 60 yr = 0
Sex	Male = 0, Female = 1
Medical insurance type	New rural cooperative medical insurance = 1
	Medical insurance for urban workers = 0
Anxiety	Yes = 1, No = 0
Depression	Yes = 1, No = 0

Table 5 Analysis of sleep disorders in patients with coronary heart disease using multiple logistic regression models

Variable	β value	SE	Wals χ^2	OR value	95%CI	*P* value
Sex	0.989	0.338	8.548	2.688	1.385-5.215	0.003
Age in yr	-0.108	0.342	0.099	0.898	0.459-1.755	0.753
Medical insurance type	1.176	0.338	12.098	0.001	1.671-6.291	0.001
Anxiety	2.219	0.380	34.020	9.200	4.365-19.394	< 0.001
Depression	2.157	0.493	19.143	8.647	3.290-22.726	< 0.001
Constant	-2.160	0.383	31.714	0.115		< 0.001

CI: Confidence interval; OR: Odds ratio; SE: Standard error.

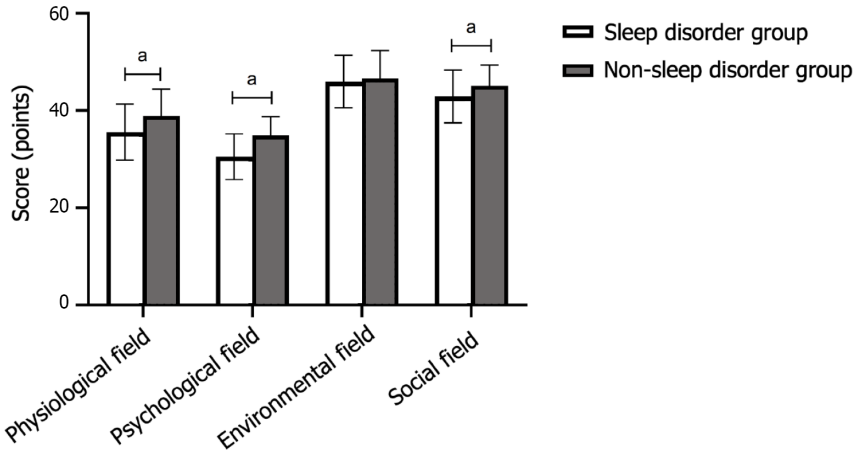
Table 6 Correlation between sleep disorders and quality of life, depression, and anxiety

Group	*r* value	*P* value
SAS	0.500	< 0.001
SDS	0.493	< 0.001
Physiological field	-0.215	< 0.001
Psychological field	-0.434	< 0.001
Environmental field	-0.080	0.217
Social relations	-0.198	0.002

SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

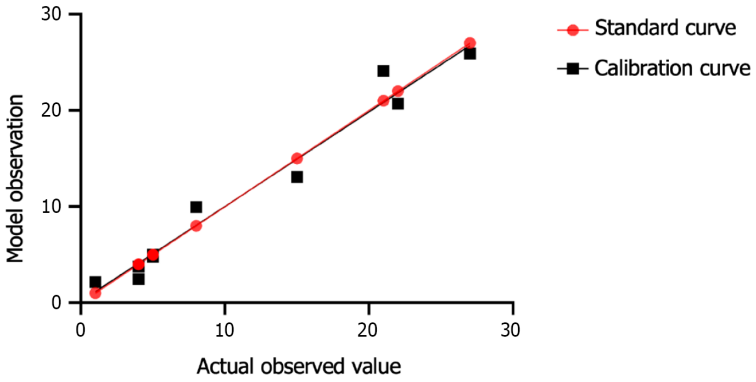
mental factors can affect the sleep quality of CHD patients. In this study, 46.67% of 240 CHD patients had sleep disorders, accounting for a relatively high proportion. Sleep disorders in CHD patients are very serious and should be paid attention to. In this study, CHD patients with sleep disorders had higher SAS and SDS scores than CHD patients without sleep disorders, and their QoL scores were substantially lower than those of patients without sleep disorders, showing that sleep disorders can have an impact on a patient's psychological health and QoL.

Multivariate logistic regression analyses showed that females, new rural cooperative medical insurance, depression, and anxiety were independent risk factors for sleep disorders in individuals with CHD ($P < 0.05$). According to research by Ulander *et al*[11], women are more prone than men to experience sleep disorders. According to Wang *et al*[12], female cancer patients have an increased incidence of sleep disorders. In line with the aforementioned study, these findings



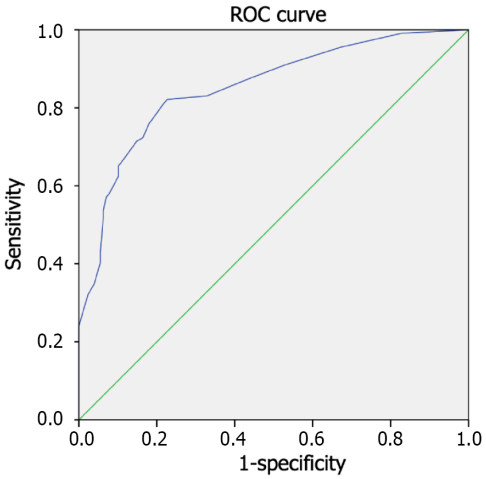
DOI: 10.5498/wjp.v13.i10.732 **Copyright** ©The Author(s) 2023.

Figure 2 Comparison of both groups' quality of life scores. [a]*P* < 0.05 *vs* non-sleep disorder group.



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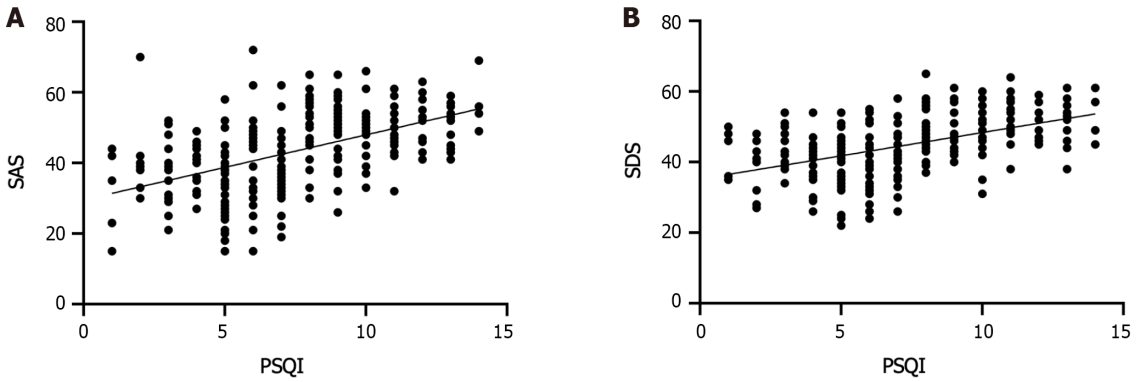
Figure 3 Calibration degree of the logistic regression model.



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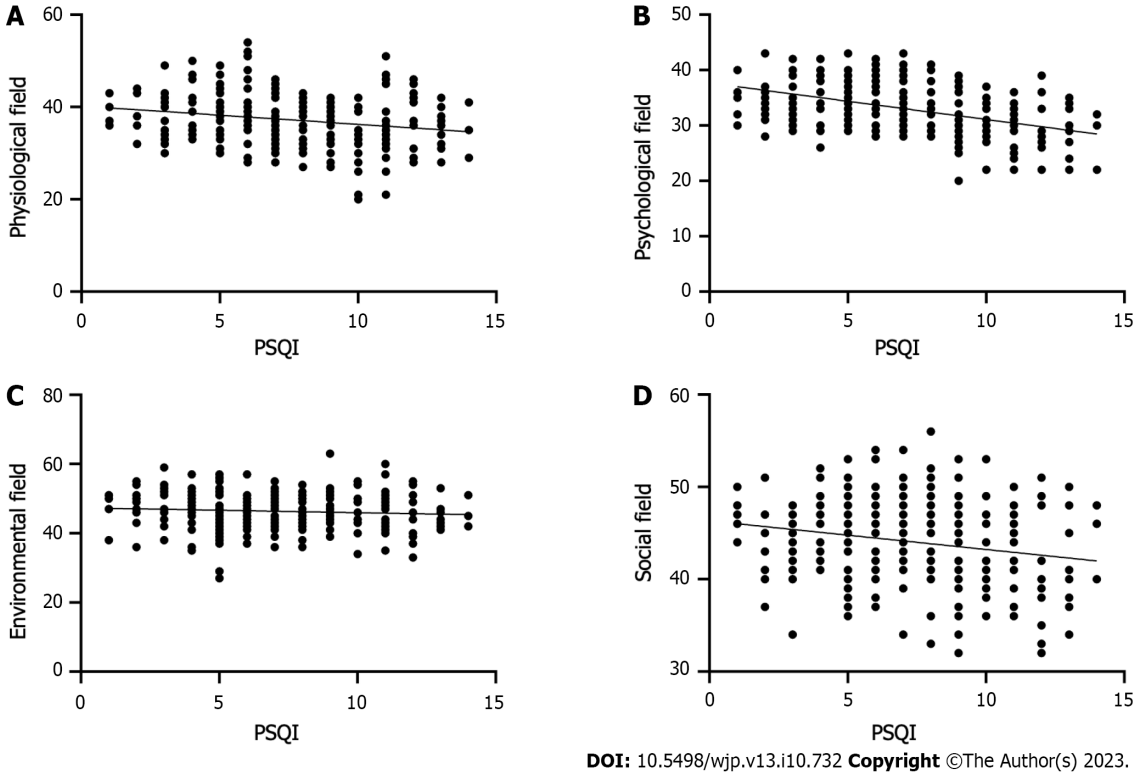
Figure 4 Prediction efficiency of the logistic regression model. ROC: Receiver operating characteristic.

support the previous study by showing that sex is a definite risk factor for anxiety problems in patients with CHD. It is speculated that the reason may be that female patients are more sensitive, their mood is easy to fluctuate, and their sleep quality is easy to be affected. The specific reason needs to be further explored. Most patients with the new rural cooperative medical insurance are rural patients. They are not as economically secure as patients in metropolitan areas, and there are disparities in the payment rates between the employee medical insurance and the new rural cooperative medical insurance, which adds to the financial strain on patients and their families and impairs patient sleep. The new



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Figure 5 Correlation between sleep disorders and anxiety and depression. A: Pittsburgh sleep quality index (PSQI) is correlated with physiological field; B: The correlation between PSQI and self-rating depression scale. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.



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Figure 6 Correlation between sleep disorders and quality of life. A: Pittsburgh sleep quality index (PSQI) is correlated with physiological field; B: PSQI is related to psychological field; C: Correlation between PSQI and environmental field; D: Correlation between PSQI and social field.

rural cooperative medical insurance is thus a significant risk factor for sleep problems in CHD patients in this study.

Sejbuk *et al*[9] reported that anxiety is a negative factor affecting sleep quality. Bonanni *et al*[13] also believe that depression and anxiety are related to menopause insomnia. Anxiety and depression were found to be independently associated risk factors for sleep disorders in this investigation, which was similar to previous research findings. CHD patients have serious physical discomfort and reduced QoL, and their strong concern for prognosis is easy to affect sleep quality. Long-term sleep disorders can lead to increased blood pressure, cardiovascular system dysfunction and neurological dysfunction, and further, aggravate psychological stress[14,15]. By contrast, anxiety, depression, and other adverse emotions can seriously affect the endocrine of patients, causing body discomfort symptoms such as palpitation and chest tightness, further affecting sleep and leading to sleep disorders[16-18]. To increase the quality of their sleep, patients with depression and anxiety should receive psychological treatment, while female CHD patients and CHD patients with new rural cooperative medical insurance should receive clinical attention. A sleep disorder prediction model was developed using multivariate logistic regression, and its prediction performance was assessed using the ROC curve. This prediction model's AUC value was 0.851 (95%CI = 0.803-0.900), showing that it has a strong predictive value for sleep problems in CHD patients.

Sleep disorder is a process of dual physiological and psychological disorders[19], and some anxiety and depression patients tend to shift more attention to sleep problems, trying to improve physiological and psychological disorders by adjusting sleep, but they are more likely to be nervous, and further aggravate sleep disorders, forming a vicious cycle. Long-term anxiety, depression and sleep disorders cause and affect each other, seriously affecting patients' work and life, and in severe cases, it may lead to functional disorders and further reduce the QoL. In addition, sleep disorders are one of the main characteristics of depression, mainly manifested by early waking, difficulty in maintaining sleep, and waking dysthymic tendencies. Serious anxiety and depression can cause psychological stress and lead to autonomic nervous disorder, and the wake-up system of the brain related to sleep and the hypnotic system is in an unbalanced state, and the excitation of the wake-up system will further lead to sleep disorders[20-22].

Adverse emotions such as anxiety and depression before bedtime can promote the activity of the reticuloendothelial system, promote the release of norepinephrine, enhance the activity of the body, and cause sleep disorders. In this study, the Spearman's correlation study showed that sleep quality was inversely correlated with the physiological field, psychological field, and social relations in QoL and positively associated with SAS and SDS. This finding implies that patients with sleep disorders should focus on enhancing their poor mood and QoL to prevent an unnecessary vicious cycle that negatively affects their prognosis. The shortcoming of the present work is that it included too few influencing factors and could not identify the reason for the high incidence of sleep disorders. Besides, it only used SAS and SDS scales to conduct a simple psychological assessment of patients, and in-depth structured psychological interviews are not conducted, which may lead to bias in survey results. Therefore, it is necessary to increase the analysis of influencing factors for further and in-depth exploration.

CONCLUSION

In summary, risk variables for sleep disturbances in CHD patients include sex, new rural cooperative medical insurance, depression, and anxiety. The risk factor prediction model established by multivariate logistic regression has good predictive efficacy. The considerable inverse relationship between sleep disorders and QoL and the substantial positive relationship between sleep disorders and depression and anxiety suggests that individuals may be able to improve their depressive moods through psychological counselling and break the vicious cycle of mutual influence between a bad mood and sleep quality. In terms of economic pressure, cost-effective treatment programs can be selected for patients as far as possible to reduce the economic pressure on patients' families, which is conducive to improving their bad mood, improving their sleep quality and QoL, and improving their prognosis.

ARTICLE HIGHLIGHTS

Research background

Studies have shown that sleep disorders are closely related to anxiety and depression, and the quality of life (QoL) of patients with sleep disorders is generally poor. The significance of this study is to explore the status quo and risk factors of sleep disorders in patients with coronary heart disease (CHD) and their correlation with anxiety, depression and QoL. To provide reference for the prevention and treatment of sleep disorders in clinical CHD.

Research motivation

The current status of sleep disorders in patients with CHD is the main topic of this study. At present, it is clinically necessary to explore the current status of sleep disorders in patients with CHD and its correlation with anxiety, depression and QoL, so as to provide reference for the prevention and treatment of patients with CHD sleep disorders. The significance of this study is to explore the risk factors of patients with CHD sleep disorders and their correlation with anxiety, depression and QoL, encourage clinical teams to continue to explore CHD sleep disorders, and promote the continuous progress of sleep disorder prevention and treatment technology.

Research objectives

The incidence of sleep disorders in patients with CHD was 46.67%. Sex, female, new rural cooperative medical insurance, anxiety and depression were independent risk factors for CHD sleep disorders. It was confirmed that CHD sleep disorders were closely related to anxiety, depression and QoL, providing a new reference for clinical prevention and treatment of CHD sleep disorders in the future.

Research methods

The clinical data of patients were retrospectively analyzed, and the patients were divided into the sleep disorder group and the non-sleep disorder group according to their sleep conditions. The general data of the two groups were statistically analyzed by independent sample *t*-test and χ^2 test. The risk factors of sleep disorders in patients with CHD were analyzed by the logistic multivariate regression method and a risk prediction model was built. Receiver operating characteristic was used to analyze the effectiveness of the risk prediction model, and Spearman's correlation was used to analyze the correlation between sleep disorders and anxiety, depression, and QoL.

Research results

Patients with CHD sleep disorder are closely related to anxiety, depression and QoL, and sex, female, new rural medical insurance, anxiety and depression are risk factors for patients with CHD sleep disorder, providing a new reference for the prevention and treatment of patients with CHD sleep disorder. It is necessary to further expand the sample size to explore the influencing factors of patients with CHD sleep disorder.

Research conclusions

Patients with CHD sleep disorders can interact with anxiety and depression, forming a vicious circle, so clinical attention should be paid to psychological intervention for patients with CHD sleep disorders.

Research perspectives

Sleep disorders in patients with CHD are closely related to anxiety and depression, which can have a negative impact on QoL. Emotional intervention methods can be used to improve sleep disorders and QoL in patients with CHD.

FOOTNOTES

Author contributions: Zheng D initiated the project and designed the experiment; Tan RJ conducted the clinical data collection; Liu W performed postoperative follow-up and recorded the data; Song PC conducted a number of collation and statistical analyses; Li FD wrote the original manuscript and revised the paper; All authors read and approved the final manuscript.

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Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Hengshui People's Hospital.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

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Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Clinical value of ankle flexion and extension exercises combined with a psychological intervention in knee osteoarthritis

Yang Liu, Rong Chen, Yang Zhang, Qin Wang, Jiang-Li Ren, Chang-Xu Wang, Yuan-Kun Xu

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Abstract

BACKGROUND

Considering the limited effectiveness of clinical interventions for knee osteoarthritis (KOA), it is necessary to continue to explore appropriate and effective treatment strategies to improve the condition of KOA patients.

AIM

To clarify the influence of ankle flexion and extension exercises combined with a psychological intervention on the psychological status and activities of daily living (ADLs) of patients with KOA.

METHODS

The research participants were 116 KOA patients admitted to The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between May 2019 and May 2022, including 54 patients receiving routine treatment, care and psychological intervention (control group) and 62 patients additionally treated

with ankle flexion and extension exercises (research group). The two groups were comparatively analyzed in terms of psychological status (Self-rating Anxiety/Depression Scale, SDS/SAS), ADLs, knee joint function (Lysholm Knee Scoring Scale), pain (Visual Analog Scale, VAS), fatigue (Multidimensional Fatigue Inventory, MFI), and quality of life (QoL; Short-Form 36 Item Health Survey, SF-36).

RESULTS

After evaluation, it was found that the postinterventional SDS, SAS, VAS, and MFI scores in the research group were significantly reduced compared with the baseline (before the intervention) values and those of the control group, while the postinterventional Lysholm, ADL and SF-36 scores were markedly elevated.

CONCLUSION

Therefore, ankle flexion and extension exercises are highly effective in easing negative psychological status, enhancing ADLs, daily living ability, knee joint function and QoL, and relieving pain and fatigue in KOA patients, thus warranting clinical promotion.

Key Words: Ankle flexion and extension exercises; Knee osteoarthritis; Psychology; Negative emotions; Activities of daily living; Quality of life

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Core Tip: This study explores and verifies the clinical advantages of ankle flexion and extension exercises combined with a psychological intervention in knee osteoarthritis from the aspects of negative mood, activities of daily living, knee function, pain, fatigue, and quality of life.

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INTRODUCTION

Knee osteoarthritis (KOA) is a chronic, inflammatory and degenerative joint disease that predominates in middle-aged and elderly women and is pathologically characterized by cartilage degeneration and bone overgrowth (osteophyte and subchondral thickening)[1-3]. KOA patients suffer from joint pain, swelling, stiffness, deformity, and dysfunction, which not only negatively affect patients' activities of daily living (ADLs) to varying degrees but also cause psychological distress to patients, affecting their quality of life (QoL); hence, it is also paramount to intervene in patients psychologically[4,5]. An in-depth analysis of the causes of KOA revealed that abnormal joint loads such as excessive exercise and past sprains, mechanical injuries, age, obesity, diet and genetic factors are factors that increase the risk of developing KOA[6]. According to epidemiological data, KOA is one of the important causes of lower-limb disability in the elderly population and may affect 40% of men and 47% of women, with an incidence of 60% among middle-aged and elderly individuals[7,8]. The pathogenesis of KOA is complicated. Although many attempts have been made to suppress the course of KOA, it is still necessary to continue to explore suitable and effective treatment strategies to improve the condition of KOA patients.

There are many clinical treatment options for KOA, including weight loss, exercise, painkillers, intra-articular hyaluronic acid, and joint replacement surgery[9]. Weight loss is mainly applicable to obese patients, while analgesics, intra-articular hyaluronic acid, and joint replacement surgery carry certain medication or surgical risks, especially for elderly patients with serious diseases[10]. Therefore, this study included an in-depth exploration of therapeutic strategies for KOA patients from the perspective of exercise. Exercise therapy, as a lifestyle intervention, mainly strengthens blood circulation by regulating venous reflux and congestion, thus increasing joint range of motion and muscle strength while positively influencing joint stability[11,12]. Ankle flexion and extension exercise is an exercise mode mainly based on ankle plantar flexion and ankle dorsiflexion, which has a positive effect on lower-limb blood circulation and muscle strength[13]. A report suggests that passive ankle flexion and extension exercises in elderly KOA patients can significantly resolve symptoms and pain with a certain degree of safety, suggesting the clinical application potential of this exercise program.

Considering that there are few studies on the clinical application of ankle flexion and extension exercises combined with a psychological intervention in KOA, this study evaluated the potential clinical value of these interventions from the aspects of psychology and ADLs.

MATERIALS AND METHODS

Patient source

The study population comprised 116 KOA patients admitted to The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between May 2019 and May 2022, including 54 patients receiving routine treatment and nursing (control group) and 62 patients additionally given ankle flexion and extension exercises (research group). The two patient groups did not differ much in baseline data and had clinical comparability ($P > 0.05$).

Criteria for patient enrollment and exclusion

Inclusion criteria were as follows: in accordance with the diagnostic criteria for KOA[14]; primary disease; intermittent joint narrowing, subchondral osteosclerosis, or cystic degeneration shown by radiographs; complete medical records; normal comprehension and expression ability; and high compliance.

The exclusion criteria were as follows: history of knee joint trauma or surgery; knee joint redness, swelling, heat pain, and obvious limitation of motion; complications with other serious chronic diseases that are not suitable for routine functional exercise; and cardio-cerebrovascular diseases, malignant tumors, or coagulation dysfunction.

Methods

The control group received routine therapy. A comfortable hospitalization environment was provided for patients. Meanwhile, nursing staff patiently addressed the doubts and concerns of patients and their families and provided vital sign monitoring, dietary guidance, psychological care, health education, nursing-patient interaction, and local massage. In addition, patients were informed of matters to be noted during the convalescence period to prevent and control the occurrence of complications and were assisted in relieving limb symptoms and reducing the pain of the primary lesion as much as possible. The psychological intervention is described below. First, relevant health education was carried out, and the etiology of KOA and the mechanism and purpose of the treatment were explained to patients in plain language to enhance their disease awareness and better understand the treatment methods, thus improving their cooperation as much as possible. Second, by enumerating patients who experienced positive outcomes (patients who experienced an ideal curative effect after following the doctor's advice) and patients who experienced negative outcomes (patients who experienced unsatisfactory curative effects due to noncompliance with the doctor's advice), the patients developed a greater realization of the importance and necessity of following the doctor's advice. Third, during the treatment, medical staff actively asked patients about their treatment feelings to optimize patients' treatment experience and find potential problems in time to give reasonable suggestions. Patients' psychological status was also considered, and psychological counseling was given in a timely manner. Moreover, the hospital provided a quiet and comfortable environment for patients so that they could take the initiative to receive diagnosis and treatment.

In addition to the measures implemented in the control group, the research group was also treated with cognitive education and ankle flexion and extension exercises. The cognitive education intervention is described below. Health and KOA-related cognitive education was conducted through multimedia lectures, mainly teaching the characteristics, functions, pathological mechanisms, risk factors and treatment methods of KOA, so that patients could understand the therapeutic value and mechanism of exercise therapy in KOA. Ankle flexion and extension exercise methods were as follows: (1) Supine ankle flexion and extension: The patient took the supine position with toes pointing to the ceiling as the starting position; the ankles were flexed and kept in that position for 10 s, followed by ankle dorsolateral extension that was maintained for 10 s before returning to the initial posture. The above exercises were performed for 20 repetitions per set with 5 sets per session and a 1-min break between sets; (2) Ankle flexion and extension in the seated position: The patient sat on the chair, with feet flat on the ground and toes pointing straight ahead; ankle plantar flexion of both feet was performed for 10 s, followed by ankle dorsiflexion for 10 s; finally, the patient returned to the initial posture. The above exercises were performed for 20 repetitions per set with 5 sets per session and a 1-minute rest between sets; and (3) Ankle flexion and extension in the standing position: The patient took a comfortable standing posture with one or both hands placed on the table or wall for support; foot plantar flexion followed by ankle dorsiflexion was performed; finally, the patient returned to the initial posture. The above exercises were performed for 10 repetitions per set with 5 sets per session and a 1-min break between sets. The ankle flexion and extension exercises in these three positions were performed in turn, that is, supine ankle flexion and extension on the first day, seated ankle flexion and extension on the second day, and standing ankle flexion and extension on the third day. Both groups were treated for three months.

Outcome measures

Psychological state. We used the Self-rating Depression/Anxiety Scale (SDS/SAS)[15] to evaluate patients' depression and anxiety before and after the intervention. Both scales have 20 items and a score range of 0-80 points, with the scores in direct proportion to the patient's depressive and anxious symptoms.

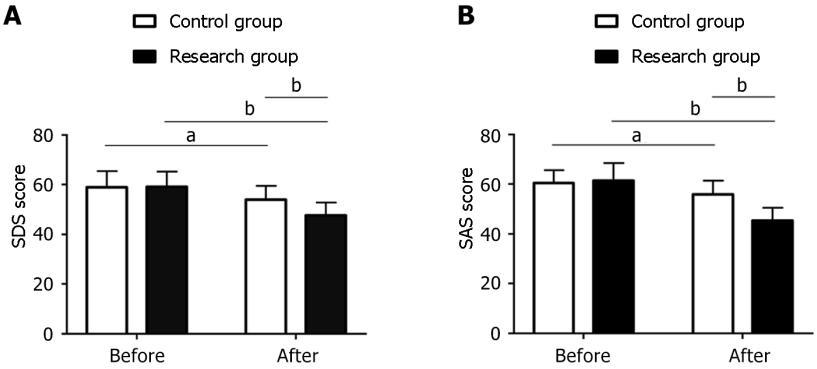
ADLs. Patients were evaluated before and after the intervention using the ADL Scale[16] for feeding, bathing, dressing, decorating, continence, and toileting domains, with a maximum score of 100. A higher score suggests a more significant improvement in patients' ADLs.

Knee joint function. Knee joint function assessment was made before and after treatment using the Lysholm Knee Scoring Scale[17], with the evaluation contents including pain, swelling, limping, blocking, instability, crouching, and climbing stairs. On a 100-point scale, higher scores are associated with better recovery of knee function.

Degree of pain. Before and after the intervention, patients were also assessed by the Visual Analog Scale (VAS; score range: 0-10)[18] to determine the degree of pain. The score is directly proportional to the degree of pain.

Table 1 Analysis of baseline data of knee osteoarthritis patients in the two groups

Factors	Control group (n = 54)	Research group (n = 62)	χ^2/t value	P value
Age (yr)	59.46 ± 6.95	58.55 ± 6.82	0.711	0.479
Sex (male/female)	25/29	27/35	0.894	0.466
Disease course (yr)	5.20 ± 2.55	5.37 ± 2.67	0.349	0.728
Single knee disease (yes/no)	38/16	41/21	0.813	0.269
Cause of illness (excessive exercise/sprain/others)	25/19/10	29/21/12	0.406	0.705
Education level (junior high school and below/senior high school and above)	34/20	38/24	0.404	0.725



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Figure 1 Analysis of the influence of ankle flexion and extension exercises on knee osteoarthritis patients' psychological state. A: The research group had a postinterventional Self-Rating Depression Scale score that was lower than the preinterventional value and that of the control group; B: The research group had a postinterventional Self-Rating Anxiety Scale score that was lower than the preinterventional value and that of the control group. Note: $^aP < 0.05$; $^bP < 0.01$. SDS: Self-Rating Depression Scale; SAS: Self-Rating Anxiety Scale.

Fatigue. The fatigue of patients before and after the intervention was evaluated by the Multidimensional Fatigue Inventory (MFI)[19], a tool with a score ranging from 20 to 100 that is positively related to fatigue.

QoL. Finally, we assessed patients' QoL from eight dimensions [physical functioning (PF); role-physical (RP); bodily pain (BP); social functioning (SF); general health (GH); mental health (MH); role-emotional (RE), and vitality (VT) by referring to the Short-Form 36 Item Health Survey (SF-36)]. Each dimension has a score of 0-10 that is positively correlated with QoL.

Statistical methods

The mean ± SEM was used to describe the measurement data, and the independent-samples t-test was used to compare two sets of measurement data. The intergroup comparison of count data expressed by percentages (%) was made by the χ^2 test. Data analysis was performed using SPSS 19.0, and the significance threshold was $\alpha = 0.05$.

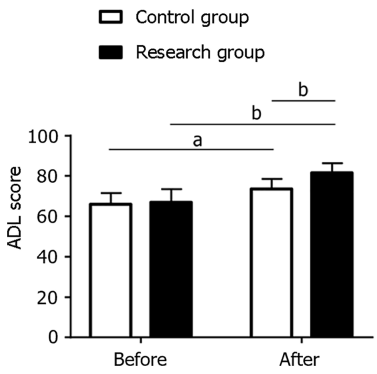
RESULTS

Analysis of baseline data of KOA patients in the two groups

Baseline data such as age, sex, course of disease, single knee disease, cause of disease and education level of KOA patients in the two groups were compared and analyzed, and no significant differences were found ($P > 0.05$). See Table 1.

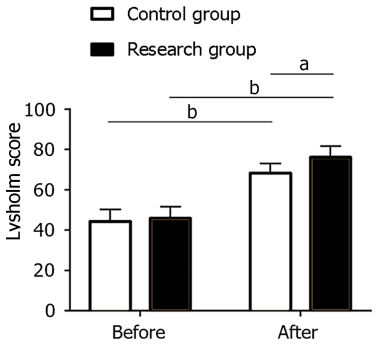
Analysis of the influence of ankle flexion and extension exercises on KOA patients' psychological state

We evaluated patients' negative psychological state by using the SDS and SAS. The results showed no significant difference in the two scale scores between the research and control groups prior to intervention [SDS: (59.15 ± 6.05) score *vs* (58.91 ± 6.44) score, SAS: (61.34 ± 7.13) score *vs* (60.37 ± 5.31) score, $P > 0.05$]. An obvious reduction in both scales was found in the two groups after the intervention [SDS: (47.60 ± 5.21) score *vs* (54.02 ± 5.51) score, SAS: (45.32 ± 5.16) score *vs* (55.83 ± 5.62) score, $P < 0.05$], especially in the research group ($P < 0.05$). See Figure 1.



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Figure 2 Analysis of the impact of ankle flexion and extension exercises on knee osteoarthritis patients' activities of daily living. The research group had a postinterventional activities of daily living score that was lower than the preinterventional value and that of the control group. [a]*P* < 0.05; [b]*P* < 0.01. ADL: Activities of daily living.



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Figure 3 Analysis of the influence of ankle flexion and extension exercises on knee osteoarthritis patients' knee joint function. The research group had a postinterventional Lysholm score that was higher than the preinterventional value and that of the control group. [a]*P* < 0.05; [b]*P* < 0.01.

Analysis of the impact of ankle flexion and extension exercises on KOA patients' ADLs

KOA patients' ADLs were assessed by the ADL scale. The ADL score did not differ markedly between the groups prior to intervention (66.97 ± 6.53) score *vs* (65.98 ± 5.65) score, $P > 0.05$), but it was elevated in both groups after the intervention (81.44 ± 4.95) score *vs* (73.50 ± 5.13) score, $P < 0.05$), with a higher postinterventional score in the research group ($P < 0.05$). See Figure 2.

Analysis of the influence of ankle flexion and extension exercises on KOA patients' knee joint function

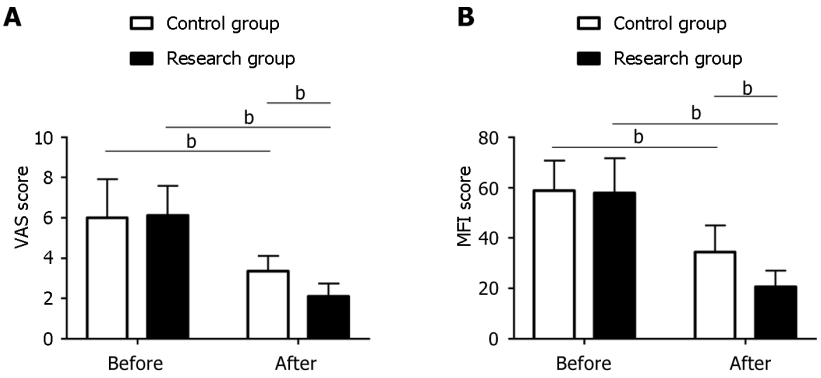
Knee function was assessed in both groups of KOA patients using the Lysholm Knee Scoring Scale. The two groups also showed similar Lysholm scores before the intervention (45.89 ± 5.69) score *vs* (44.43 ± 5.79) score, $P > 0.05$. An evident elevation in the Lysholm score was found in both arms after the intervention, with an even higher score in the research group (76.40 ± 5.25) score *vs* (68.39 ± 4.74) score, $P < 0.05$. See Figure 3.

Analysis of the impact of ankle flexion and extension exercises on pain and fatigue in KOA patients

By evaluating the VAS and MFI scores of both groups, the pain and fatigue status of KOA patients were determined. VAS and MFI scores were found to be similar in the two groups before the intervention [VAS: (6.11 ± 1.47) score *vs* (6.00 ± 1.91) score, MFI: (57.87 ± 13.85) score *vs* (58.81 ± 11.94) score, $P > 0.05$], but they were significantly reduced after the intervention, with even lower scores in the research group [VAS: (2.11 ± 0.63) score *vs* (3.35 ± 0.76) score, MFI: (20.55 ± 6.61) score *vs* (34.48 ± 10.50) score, $P < 0.05$]. See Figure 4.

Analysis of the impact of ankle flexion and extension exercises on KOA patients' QoL

The QoL of KOA patients in both groups was evaluated using the SF-36 scale. The data revealed no significant difference in SF-36 scores between the research and control groups before the intervention ($P > 0.05$). The SF-36 scores of both arms showed a significant upward trend after the intervention ($P < 0.05$), with a more significant increase in the research group ($P < 0.05$). See Figure 5.



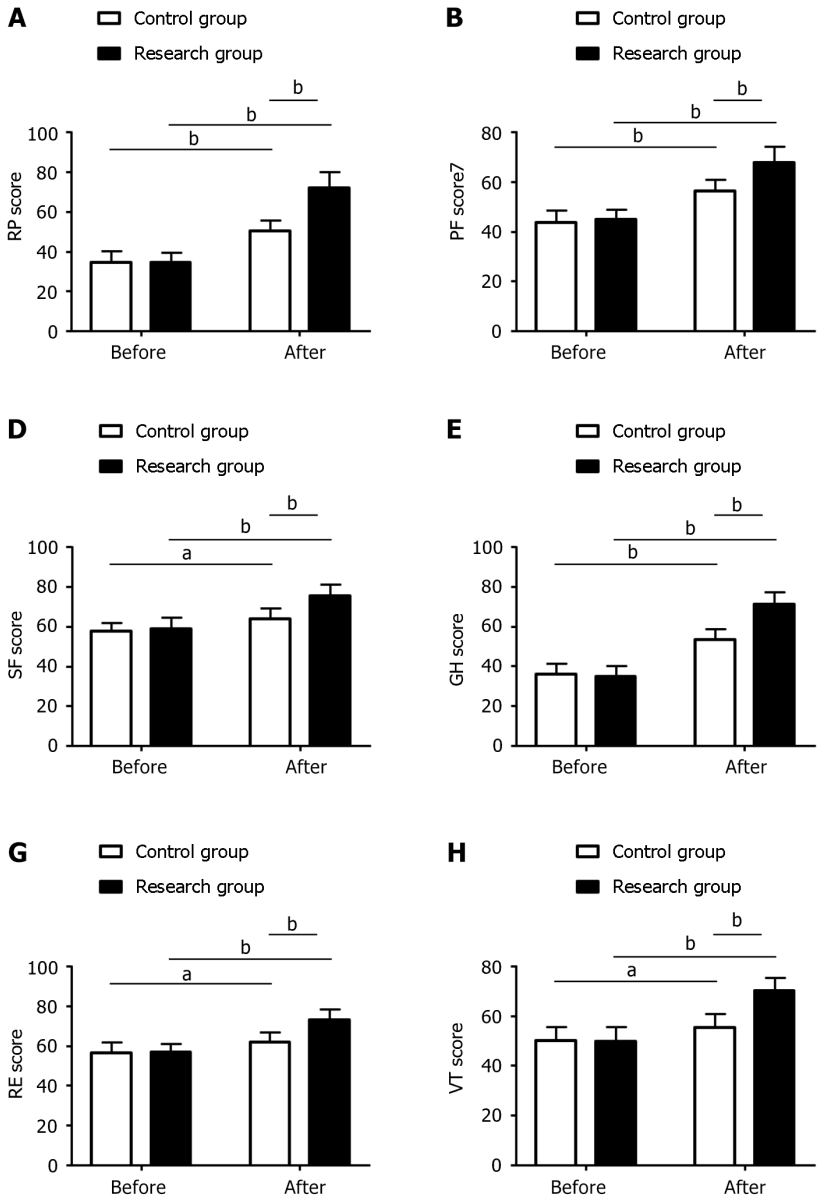
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Figure 4 Analysis of the impact of ankle flexion and extension exercises on knee osteoarthritis patients' pain and fatigue. A: The research group had a postinterventional Visual Analog Scale score that was lower than the preinterventional value and that of the control group; B: The research group had a postinterventional MFI score that was lower than the preinterventional value and that of the control group. $^{a}P < 0.05$; $^{b}P < 0.01$. VAS: Visual Analog Scale; MFI: Multidimensional Fatigue Inventory.

DISCUSSION

KOA, with complex pathological mechanisms and triggers that are not fully understood, has no effective treatment at present[20]. Ankle flexion and extension exercises, as a type of exercise rehabilitation therapy, integrate and apply the knowledge of sports medicine, rehabilitation medicine, biomechanics and modern functional anatomy to provide KOA patients with an evidence-based exercise intervention[21]. In the research of Abbott *et al*[22], exercise therapy was proven to be beneficial to physical function recovery in KOA patients, suggesting the potential value of ankle flexion and extension exercises in KOA. In another study, exercise therapy was more effective in treating KOA than conventional therapy, contributing to more significant pain reduction and improved function and QoL[23]. Psychological intervention is a measure centered on patients' psychological state and emotional experience, which can improve patients' functional outcomes by eliminating or alleviating their psychological distress[24]. Previous studies have shown that psychological intervention can play a positive role in reducing the severity of KOA symptoms and improving life satisfaction by establishing a positive attitude toward illness[25].

According to the negative psychological state investigation in this study, the research group had markedly reduced SDS and SAS scores after the intervention, which were lower than those of the control group, suggesting that ankle flexion and extension exercises combined with a psychological intervention have a good regulatory effect on the negative psychological state of KOA patients. Song *et al*[26] reported that modified Tai Chi exercises, as a kind of kinesitherapy, can significantly relieve anxiety and depression in elderly female patients with KOA, similar to our findings. Negative emotions such as anxiety and depression in KOA patients have been shown to be related to factors such as high pain levels[27]. In this study, the research group who received ankle flexion and extension exercises experienced a significant reduction in pain levels after the intervention, which may help explain its relieving effect on negative emotions. Furthermore, in the investigation of ADLs, the research group showed a postinterventional ADL score that was evidently higher than the baseline and that of the control group, indicating that ankle flexion and extension exercises combined with a psychological intervention are beneficial to significantly improve the ADLs of KOA patients. This may be attributed to the improvement in muscle strength and range of motion in patients after ankle flexion and extension exercises, thus reducing activity limitations in such patients[28]. Subsequently, knee function analysis revealed markedly increased Lysholm scores in the research group that were higher than those in the control group after the intervention, which indicates that ankle flexion and extension exercises combined with a psychological intervention are conducive to enhancing the knee joint function of KOA patients. Exercise therapy, such as ankle flexion and extension exercises, has also been reported to alleviate KOA by enhancing muscle strength, restoring neuromotor control and improving the range of joint motion[29]. Later, the analysis of pain and fatigue showed marked reductions in VAS and MFI scores in the research group that were significantly lower than those in the control group, demonstrating that ankle flexion and extension exercises combined with a psychological intervention are significantly effective in mitigating pain and fatigue in KOA patients. Peeler *et al*[30] noted in their study that low-load exercise for KOA patients has significant advantages in improving ADLs and knee joint function, with a potent pain-relieving effect, which can support our research results. In addition, the fatigue of KOA patients is primarily associated with pathological pain and decreased physical function[31]. The alleviation of fatigue in KOA patients may be related to the reduction of pain and improvement of body function by ankle flexion and extension exercises, which agrees with the research results reported by Casilda-López *et al*[32]. Finally, the QoL assessment showed that the SF-36 scores of the research group increased significantly after the intervention and were markedly higher than those of the control group, indicating that ankle flexion and extension exercises combined with a psychological intervention can significantly boost QoL in KOA patients.



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Figure 5 Analysis of the influence of ankle flexion and extension exercises on knee osteoarthritis patients' quality of life. A: The research group had a postinterventional Role-physical score that was higher than the preinterventional value and that of the control group; B: The research group had a postinterventional physical functioning score that was higher than the preinterventional value and that of the control group; C: The research group had a postinterventional bodily pain score that was higher than the preinterventional value and that of the control group; D: The research group had a postinterventional social functioning score that was higher than the preinterventional value and that of the control group; E: The research group had a postinterventional general health score that was higher than the preinterventional value and that of the control group; F: The research group had a postinterventional mental health score that was higher than the preinterventional value and that of the control group; G: The research group had a postinterventional role-emotional score that was higher than the preinterventional value and that of the control group; H: The research group had a postinterventional vitality score that was higher than the preinterventional value and that of the control group. $^{a}P < 0.05$; $^{b}P < 0.01$. PF: Physical functioning; RP: Role-physical; BP: Bodily pain; SF: Social functioning; GH: General health; MH: Mental health; RE: Role-emotional; VT: Vitality.

CONCLUSION

Taken together, while resulting in psychological relief and improvement of ADLs, ankle flexion and extension exercises combined with a psychological intervention can effectively restore knee joint function and mitigate pain and fatigue in KOA patients, thus playing a positive role in improving the quality of life of patients and warranting clinical promotion.

ARTICLE HIGHLIGHTS

Research background

Given the limited efficacy of clinical intervention in knee osteoarthritis (KOA), it is necessary to continue to explore appropriate and effective treatment strategies to improve the condition of KOA patients.

Research motivation

The pathogenesis of KOA is complex, and exploring effective treatment strategies is of great significance for the prevention and treatment of this disease.

Research objectives

The aim of this study is to clarify the influence of ankle flexion and extension exercises combined with psychological intervention on the psychology and activities of daily living (ADLs) of patients with KOA.

Research methods

The research participants were 116 KOA patients admitted between May 2019 and May 2022, including 54 cases receiving routine treatment, care and psychological intervention (control group) and 62 cases additionally treated with ankle flexion and extension exercises (research group) on the basis of the control group. The two groups were comparatively analyzed in terms of psychological status (Self-rating Anxiety/Depression Scale, SDS/SAS), ADLs (ADL scale), knee joint function (Lysholm Knee Scoring Scale), pain (Visual Analogue Scale, VAS), fatigue (Multidimensional Fatigue Inventory, MFI), and quality of life (QoL; Short-Form 36 Item Health Survey, SF-36).

Research results

After evaluation, it was found that the postinterventional SDS, SAS, VAS, and MFI scores in the research group were significantly reduced compared with the baseline (before the intervention) values and those of the control group, while the postinterventional Lysholm, ADL, and SF-36 scores were markedly elevated.

Research conclusions

Ankle flexion and extension exercises are highly effective in easing negative psychology, enhancing ADLs, knee joint function and QoL, and relieving pain and fatigue in KOA patients, which is worthy of clinical promotion.

Research perspectives

In addition to the positive effect on the negative psychological relief and improvement of ADLs of KOA patients, ankle flexion and extension exercises combined with a psychological intervention can also effectively restore knee joint function, alleviate pain and fatigue, and enhance patients' quality of life, providing an effective treatment option for KOA patients.

FOOTNOTES

Author contributions: Liu Y, Chen R, Zhang Y and Wang Q contributed equally to this work and are co-first authors; Liu Y, Chen R, Zhang Y and Wang Q concepted the study, supervised the study, contributed to the investigation, the visualization of the study, and originally drafted the manuscript; Xu YK collected the data; Wang CX contributed to the formal analysis; Liu Y, Chen R, Zhang Y, Wang Q and Ren JL contributed to the methodology; Xu YK validated the study; Liu Y, Chen R, Zhang Y, Wang Q and Ren JL reviewed and edited the manuscript.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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Effects of different intervention methods on psychological flexibility, negative emotions and sleep quality in chronic hepatitis B

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Abstract

BACKGROUND

Patients with chronic hepatitis B (CHB) experience various problems, including low psychological flexibility, negative emotions, and poor sleep quality. Therefore, effective nursing interventions are required to reduce adverse events. Acceptance and commitment therapy (ACT) combined with enabling cognitive-behavioral education (ECBE) can improve patients' psychological and sleep. Therefore, we speculate that this may also be effective in patients with CHB.

AIM

To investigate the effects of different intervention methods on psychological flexibility, negative emotions, and sleep quality in patients with CHB.

METHODS

This retrospective study examined clinical and evaluation data of 129 patients with CHB. Intervention methods were divided into a conventional group (routine nursing, $n = 69$) and a combination group (ACT combined with ECBE, $n = 60$). We observed changes in psychological flexibility, negative emotions, sleep quality, and self-care ability in both groups. Observation items were evaluated using the Acceptance and Action Questionnaire-2nd Edition (AAQ-II), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), and Exercise of Self-Care Agency Scale (ESCA).

RESULTS

Compared with the conventional group, the AAQ-II score of the combined group was lower ($F_{\text{between-group effect}} = 8.548$; $F_{\text{time effects}} = 25.020$; $F_{\text{interaction effects}} = 52.930$; all $P < 0.001$), the SAS score ($t = 5.445$) and SDS score ($t = 7.076$) were lower (all $P < 0.001$), as were the PSQI dimensions ($t_{\text{sleep quality}} = 4.581$, $t_{\text{fall sleep time}} = 2.826$, $t_{\text{sleep time}} = 2.436$, $t_{\text{sleep efficiency}} = 5.787$, $t_{\text{sleep disorder}} = 5.008$, $t_{\text{hypnotic drugs}} = 3.786$, $t_{\text{daytime dysfunction}} = 4.812$); all $P < 0.05$). The ESCA scores for all dimensions were higher ($t_{\text{health knowledge level}} = 6.994$, $t_{\text{self-concept}} = 5.902$, $t_{\text{self-responsibility}} = 19.820$, $t_{\text{self-care skills}} = 8.470$; all $P < 0.001$).

CONCLUSION
ACT combined with ECBE in patients with CHB can improve psychological flexibility and sleep quality, alleviate negative emotions, and improve self-care.

Key Words: Acceptance and commitment therapy; Empowerment cognitive-behavioral education; Chronic hepatitis B; Psychological flexibility; Negative emotion; Sleep quality

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Core Tip: Chronic hepatitis B (CHB) is an infectious and progressive disease requiring basic treatment supplemented with effective nursing interventions. We analyzed the clinical data of 129 patients with CHB. Acceptance and commitment therapy combined with cognitive-behavioral education improved the psychological flexibility and sleep quality of patients with CHB, relieve negative emotions, and improve self-care ability, making a breakthrough in the problem of insufficient routine care.

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INTRODUCTION

Chronic hepatitis B (CHB) is a frequent chronic infectious disease. According to the World Health Organization in 2017 [1], the number of CHB infections worldwide reached 257 million. Approximately 900000 people worldwide die each year from hepatitis B virus (HBV) infection or its complications[1]. Due to the mutual influence of physiological, psychological, and social factors, patients with CHB often have various sleep disorders, thus reducing the therapeutic effect[2]. Drug therapies such as conventional antiviral therapy combined with effective nursing interventions can control disease progression[3].

Bedside delivery of health education to the patient improves understanding and self-management[4]. However, after receiving education, patients still have an insufficient sense of participation, low mastery of disease knowledge, and no change in incorrect understandings. Additionally, their psychological and behavioural adaptation to the disease is not obvious, and most patients have unresolved problems such as anxiety, depression, and poor sleep. This is related to the lack of conventional health education and targeted psychological counselling[5]. Moreover, the lack of routine CHB care is a clinical problem that needs to be resolved.

Acceptance and commitment therapy (ACT) is a new type of cognitive behavioral therapy based on functional contextualism and relational reference theory, which promotes individual acceptance of the present and self, and increases psychological flexibility[6]. Additionally, enabling cognitive-behavioral education (ECBE) is a psychological behavior therapy that aims to explore individual-centered problems; help individuals reconstruct cognitive processes; solve emotional, cognitive, and behavioral disorders; and promote the development of skills and positive beliefs that enable the individual to effectively deal with problems associated with their disease[7]. ACT and ECBE have been applied to the nursing care of patients with diabetes[8], cancer[9], and other diseases[10] and have achieved good results. However, the combination of these two therapies has not been previous investigated in the treatment of CHB. This study explored the effects ACT combined with ECBE on psychological flexibility, negative emotions, and sleep quality in patients with CHB.

MATERIALS AND METHODS

Research object

A total of 129 patients with CHB treated at The First People's Hospital of Wenling between January 2021 and June 2022 were retrospectively selected. Patients were divided into two groups, depending on whether they received routine care or ACT combined with ECBE intervention.

The inclusion criteria were as follows: (1) Diagnosis of CHB according to the criteria; (2) normal vision and hearing function; (3) a complete record of baseline data (sex, age, disease course, and liver function); and (4) assessment of psychological flexibility, negative emotions, and sleep quality.

The diagnostic criteria for CHB included a positive results for both serum surface antigen and HBV DNA[11]. Additionally, liver function index alanine aminotransferase continually increased and liver histological examination showed hepatitis lesions.

The following exclusion criteria was applied: (1) Severe sleep disorders or insomnia caused by other diseases; (2) Combined heart, liver, kidney, and other organ lesions; (3) Viral hepatitis other than CHB; and (4) Malignant tumors.

According to the different nursing intervention methods applied, the patients were classified into a conventional group (routine nursing care, n = 69) and a combination group (ACT combined with ECBE, n = 60). The research concepts used are presented in Figure 1.

Related research data collection

We collected baseline patient data from the electronic medical records, including sex, age, disease course, and evaluation data of psychological flexibility, negative emotions, sleep quality, and self-care agency.

Detailed intervention methods

Routine nursing: Based on principles of nursing practice, nursing staff provided nutritional interventions, medication guidance and safety nursing, early rehabilitation training, and relevant health education. Health education for patients with CHB was delivered through one-to-one communication or distribution of educational manuals to disseminate knowledge on the causes of CHB, treatment methods, risk factors, and other aspects of the disease. Relevant psychological counseling; daily personal self-care skills in a home setting and life guidance were discussed with patients on discharge from hospital.

ACT: Acceptance perception: Medical staff provided health education using graphic publicity pages or short videos to inform patients of the pathogenesis, routine treatment options, and precautions of CHB, to help increase understanding of CHB and the ramifications of the disease.

Cognitive disengagement: Family members were guided to encourage patients to actively cooperate with drug treatment or psychotherapy and strengthen family awareness of CHB to reduce the impact of adverse events or negative emotions. Under the guidance of nutritionists, dietary management and stress reduction training was also strengthened to adjust patients' negative emotions.

Experience life: Patients were encouraged to exchange experiences with their friends to can share the burden of disease and integrate into surrounding life and work. The encouragement and support of family and patient friends enabled patients to develop a good understanding of their disease and alleviate negative emotions such as fear, anxiety, and depression. Patients were also encouraged to share their experiences and empathize with life experiences, diverting patients' attention.

Self-awareness: Through patient communication and doctor-patient communication, patient awareness of the disease was strengthened, establishing confidence in treating the disease to establish correct cognition and attitude and understanding the disease.

Values: With the support of family members and medical staff, patients established social values, adjusted their mentality, returned to society and work, and developed positive attitudes towards life.

Positive coping: Through drug treatment, psychological intervention, and moderate exercise, patients strengthened their confidence, modified negative emotions, and actively cooperated with treatment.

ECBE: Clarify themes and processes: To understand the most harmful, extensive, and high-incidence problems and in CHB care, the nursing content included identifying problem(s), expressing feelings, setting goals, and making plans.

Clarify patient needs (problem establishment): Patient's thoughts and educational needs, such as changes during illness, daily mood and reasons, family support and care, disease knowledge, support, and help were identified.

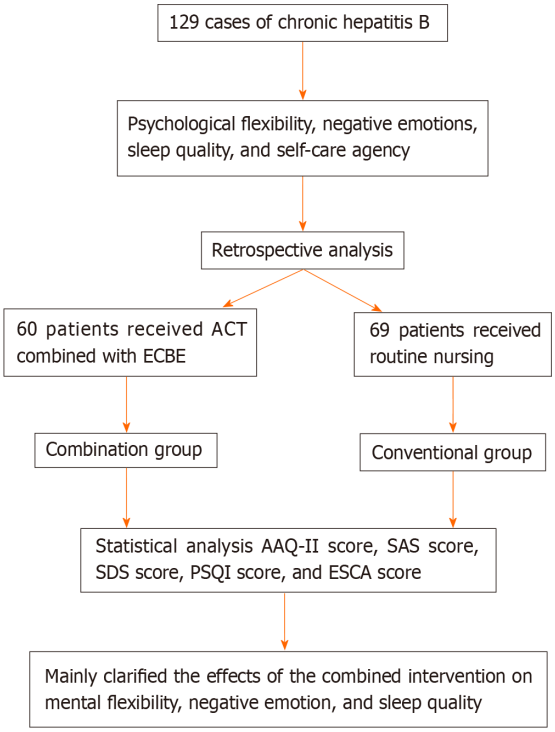
Scale assessments: Acceptance and Action Questionnaire-2nd Edition (AAQ-II), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), Exercise of Self-Care Agency Scale (ESCA), and Master of psychological flexibility, negative emotions, sleep quality, and self-care abilities scores were observed.

Goal setting Cognitive aspects: (1) CHB Education. By playing videos, issuing manuals or one-on-one communication, and conducting collective lectures, patients could fully understand the harm caused by CHB, importance of a good mentality, importance of drug treatment, and side effects; and (2) diet education. Based on the health belief model[12], a reasonable diet knowledge education plan was developed for patients to understand the importance of nutritional balance and related information. Specific information about nutritional balance for example, dietary calcium supplements (China's recommended amount of calcium is 800 mg per day), and increased fresh fruits and vegetable and protein-rich food (such as milk, poultry, fish) intake was provided. Education was delivered through videos, pictures, animations, and text.

Behavior: (1) Improved family support. Family members or spouses were included in the synchronous education program to develop basic knowledge of CHB nursing and psychological and physiological support. Family members were also instructed to create a good family atmosphere and environment, pay attention to the patients' psychological state, and provide timely counseling to reduce the negative emotions caused by loneliness and family apathy; and (2) Improve self-care. Help was provided to patients to understand the importance of self-care and prevention and treatment of common health problems in CHB. Nursing staff focused on the mental health of patients, teaching them physical and mental adjustment methods to prevent anxiety and depression.

Observation target

Psychological flexibility: Before the intervention, 3 mo after intervention, and 6 mo after, the psychological flexibility of the patients was evaluated using the AAQ-II scale[13]. The seven items were scored from 1 (never) to 7 (always) with a total score of 7-49 points. Higher scores indicated higher empirical avoidance and psychological flexibility. Cronbach's α coefficient of the scale was 0.880, indicating good reliability.



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Figure 1 Research ideas. ACT: Acceptance and commitment therapy; ECBE: Enabling cognitive-behavioral education; AAQ-II: Action Questionnaire-2nd Edition; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; PSQI: Pittsburgh Sleep Quality Index; ESCA: Exercise of Self-Care Agency Scale.

Negative emotions: The SAS and SDS[14] were used to evaluate the degree of anxiety and depression before and 6 mo after the intervention. The two scales were composed of 20 items scored according to a four-level scoring method (score 1-4 points). Higher scores indicated more severe anxiety and depression.

Sleep quality: The PSQI[15] was used to evaluate sleep quality before and after the intervention. This scale included the following seven dimensions: sleep quality, sleep time, sleep time, sleep efficiency, sleep disorders, use of hypnotic drugs, and daytime dysfunction. Each dimension was scored on a scale of 0-3 points. Higher scores indicated worse sleep quality.

Self-care ability: Before and 6 mo after the intervention[16], self-care abilities, including health knowledge (14 items), self-concept (nine items), self-responsibility (eight items), self-care skills (12 items) and four other dimensions (health knowledge level, self-concept, self-responsibility, and self-care skills). The 43 items were scored using the five-level scoring method (0-4 points). Higher scores indicated better self-care ability. Cronbach's α coefficient was 0.76-0.87, indicating good internal consistency.

Statistical analysis

SPSS 20.0 [IBM SPSS Statistics software, IBM Corp (version 20.0), NY, United States] was used to analyze the data. The data are presented as mean ± SD. The *t*-test was used to compare the difference between two sets of data. One-way analysis of variance was used to compare the two groups. The Bonferroni *t*-test was used for multiple comparisons between multiple samples. Repeated-measures analysis of variance was used to compare data at different time points between groups. The number of cases and chi-square test were used to analyze the count data. A test value = 0.05 was used. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

Baseline data such as sex, age, and course of disease were compared between the two groups. No significant differences were observed (all $P > 0.05$), indicating comparability (Table 1).

AAQ-II score

The AAQ-II score in the combination group was significantly lower than that in the conventional group. The AAQ-II scores of both groups decreased with time, with an interaction effect between group and time ($F_{\text{between-group effect}} = 8.548$; $F_{\text{time effects}} = 25.020$; $F_{\text{interaction effects}} = 52.930$; all $P < 0.001$) (Table 2).

Table 1 Basic data

Group	Gender (*n*, male/female)	Age (mean ± SD, yr)	Number of units(*n*, first visit/return visit)	Course of disease (mean ± SD, yr)		Educational level (*n*)			Child-Pugh grade	
				Course of CHB	Course of insomnia	Junior high school and below	High school	Bachelor's degree and above	Grade A	Grade B
Combination group (*n* = 60)	38/22	48.36 ± 10.25	19/41	12.25 ± 3.17	2.51 ± 0.86	15	28	17	39	21
Conventional group (*n* = 69)	41/28	49.21 ± 11.12	24/45	13.07 ± 3.58	2.22 ± 0.88	18	31	20	42	27
χ^2/t	0.207	0.449	0.140	1.368	1.887	0.041			0.234	
P	0.649	0.654	0.708	0.174	0.061	0.980			0.628	

CHB: Chronic hepatitis B.

Table 2 Action Questionnaire-2nd Edition scores

Time	Combination group (*n* = 60)	Conventional group (*n* = 69)	*t*	*P*
Before intervention	39.27 ± 6.22	38.72 ± 5.69	0.524	0.601
3 mo after intervention	31.26 ± 7.15	36.28 ± 6.67	4.123	< 0.001
6 mo after intervention	28.11 ± 6.32	33.51 ± 6.63	4.715	< 0.001
F	45.920	11.640	–	–
P	< 0.001	< 0.001	–	–

Multiple comparison results of PSQI scores at each time point between the conventional and combination groups showed significant differences in AAQ-II scores between the two time points in each group (all $P < 0.05$) (Table 3).

SAS and SDS score

The SAS scores of the combination group were 49.25 ± 5.35 and 37.56 ± 6.11, before and after intervention, respectively; $t = 11.150$, $P < 0.001$. The SDS scores were 53.58 ± 7.12 and 41.56 ± 5.38, before and after intervention, respectively; $t = 10.430$, $P < 0.001$.

The SAS scores of the conventional group were as follows: before intervention (48.68 ± 5.52), and after intervention (43.27 ± 5.79), $t = 5.618$, $P < 0.001$. The SDS scores were, before intervention (54.03 ± 6.69), after intervention (49.20 ± 6.69), $t = 4.241$, $P < 0.001$.

In comparison with the conventional group, the SAS ($t = 5.445$) and SDS ($t = 7.076$) scores of the combination group were lower after the intervention (both $P < 0.001$) (Figure 2).

PSQI score

The post-intervention scores for sleep quality, fall sleep time, sleep time, sleep efficiency, sleep disorders, use of hypnotic drugs, daytime dysfunction, and other dimensions in the combination group and the conventional group were lower than the corresponding pre-intervention scores (all $P < 0.001$). The scores for each dimension in the combination group were lower than those in the conventional group ($P < 0.05$) (Table 4).

ESCA score

The pre-intervention scores of health knowledge level, self-concept, self-responsibility, and self-care skills in the combination group were: 33.48 ± 5.36, 20.16 ± 3.25, 21.58 ± 4.39, and 31.25 ± 5.54 points. The same pre-intervention scores in the conventional group were: 34.02 ± 4.54, 20.67 ± 3.51, 21.24 ± 4.13, and 30.86 ± 6.62 points.

After the intervention, the scores of the above dimensions in the combination group were 51.27 ± 3.39, 31.25 ± 4.42, 29.17 ± 3.08, and 43.12 ± 4.24 points. The scores in the conventional group were 45.36 ± 5.73, 26.17 ± 5.24, 25.68 ± 4.42, and 35.56 ± 5.67 points.

Scores in both groups were higher after the interventions (all $P < 0.001$). The scores for each dimension in the combined group were higher than those in the conventional group (*t*: 6.994, 5.902, 5.128, and 8.470; all $P < 0.001$) (Figure 3).

Table 3 Multiple comparisons of Pittsburgh Sleep Quality Index scores at different time points (Bonferroni)

Group	(I) Time	(J) Time	Mean difference (I-J)	Standard error	*P*	95%CI	
						Lower limit	Upper limit
Combination group							
	Before intervention	3 mo after intervention	8.017	1.198	0.001	5.121	10.913
		6 mo after intervention	11.167	1.198	0.001	8.271	14.063
	3 mo after intervention	before intervention	-8.017	1.198	□0.001	-10.913	-5.121
		6 mo after intervention	3.150	1.198	0.028	0.254	6.046
	6 mo after intervention	Before intervention	-11.167	1.198	0.001	-14.063	-8.271
		3 mo after intervention	-3.150	1.198	0.028	-6.046	-0.254
Conventional group							
	Before intervention	3 mo after intervention	2.449	1.080	0.073	-0.157	5.056
		6 mo after intervention	5.217	1.080	0.001	2.611	7.824
	3 mo after intervention	Before intervention	-2.449	1.080	0.073	-5.056	0.157
		6 mo after intervention	2.768	1.080	0.033	0.162	5.375
	6 mo after intervention	Before intervention	-5.217	1.080	0.000	-7.824	-2.611
		3 mo after intervention	-2.768	1.080	0.033	-5.375	-0.162

95%CI: 95% confidence interval.

Table 4 Pittsburgh Sleep Quality Index score

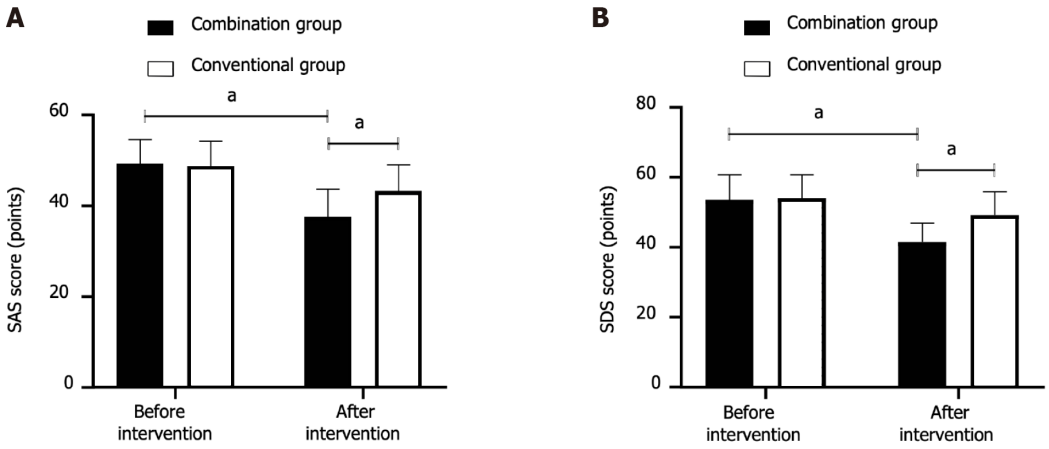
Group and time	Statistics	Sleep quality	Fall sleep time	Sleep time	Sleep efficiency	Sleep disorder	Hypnotic drugs	Daytime dysfunction
Combination group (*n* = 60)								
Before intervention		2.35 ± 0.65	2.43 ± 0.66	2.52 ± 0.61	2.33 ± 0.58	1.98 ± 0.52	2.05 ± 0.52	2.18 ± 0.54
After intervention		0.82 ± 0.42[1]	0.85 ± 0.44[1]	0.78 ± 0.48[1]	0.75 ± 0.46[1]	0.77 ± 0.52[1]	0.86 ± 0.36[1]	1.16 ± 0.31[1]
	t	15.310	15.430	17.360	16.530	12.750	14.570	12.690
	P	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Conventional group (*n* = 69)								
Before intervention		2.26 ± 0.57	2.35 ± 0.62	2.49 ± 0.64	2.29 ± 0.62	1.95 ± 0.47	2.01 ± 0.55	2.15 ± 0.56
After intervention		1.06 ± 0.35	1.06 ± 0.53	0.97 ± 0.58	1.05 ± 0.32	1.02 ± 0.37	1.02 ± 0.22	1.41 ± 0.58
	t	14.900	13.140	14.620	14.760	12.910	13.880	7.624
	P	0.001	0.001	0.001	0.001	0.001	0.001	0.001

[1]The index compared with normal group, $P < 0.05$.

DISCUSSION

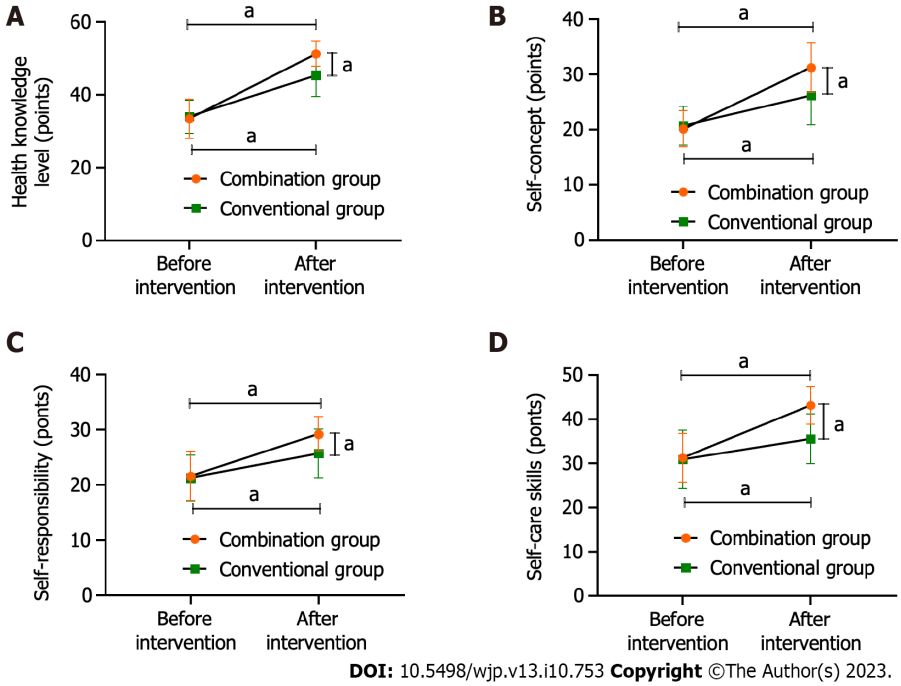
As CHB easily progresses to cirrhosis or liver cancer[17], there are considerable changes in the psychological, emotional, and living conditions of patients; effective nursing interventions are needed. Insomnia, a decline in sleep quality, is a common symptom in patients with CHB. primarily caused by an increase in endotoxin levels, unbalanced hormone secretion, and increased psychological burden which negatively impacts quality of life.

We found that the AAQ-II scores of both groups were lower after the intervention, and the combined group scores were lower, indicating that ACT combined with ECBE could reduce patient empirical avoidance behavior and enhance psychological flexibility. This is consistent with previous studies on adult patients with chronic pain [18]. Psychological



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Figure 2 Self-Rating Anxiety Scale score and Self-Rating Depression Scale score. A: The post-intervention Self-Rating Anxiety Scale score (t = 5.445); B: Self-Rating Depression Scale score (t = 7.076) in the combination group were lower than those in the conventional group (both P < 0.001). ^{a}P < 0.05. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.



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Figure 3 Exercise of Self-Care Agency Scale score. A: Health knowledge level; B: Self-concept; C: Self-responsibility; D: Self-care skills. The post-interventions scores of each dimension in the combined group were lower than those in the combination group. ^{a}P < 0.05.

flexibility refers to psychological and behavioral adaptations to changing situations during interactions between individuals and the environment[19], a protective factor for mental health[20].

CHB is characterized by progression to cirrhosis or liver cancer and a heavy economic burden, which can easily cause negative emotions and need for patients to escape and control their worries. ACT guides and encourages patients to accept all negative and positive experiences with an open and optimistic attitude. After ACT intervention, patients may no longer resist, control, or evade CHB but observe and accept it objectively. Additionally, patients with CHB can cope more effectively with the stimulation of surrounding environmental factors and take positive actions to reduce psychological pressure, anxiety and depression.

ECBE focuses on four aspects: Establishing problems, expressing emotions, setting goals, and formulating plans. It focuses on patients' psychological changes, unhealthy emotions, and sleep quality and adopts targeted interventions and supervision. ECBE also encourages patients to gradually reduce avoidance behaviours, anxiety, depression, insomnia, and other problems, improves psychological flexibility, and relieves negative emotions. Previous research[21] has demonstrated that psychological flexibility is closely related to anxiety and depression. According to the results of this study, the SAS and SDS scores of patients receiving ACT combined with ECBE nursing were significantly reduced, indicating that anxiety and depression were significantly alleviated, highlighting the effectiveness of the combined

intervention in relieving negative emotions in patients with CHB.

In this study, the scores of the PSQI were lower and ESCA scores were higher in the combination group, demonstrating that ACT combined with ECBE also played a significant role in regulating sleep quality and patient self-care ability. The sleep quality of patients with CHB is typically much lower[22]. For ACT combined with ECBE, nursing staff developed patient knowledge of CHB and helped to correct misunderstandings about the disease, reducing excessive worrying and negative emotions, and improving sleep quality.

Moreover, the low self-care ability of patients with CHB has been demonstrated[23]. Improving self-care ability is the final step in the implementation of ECBE. Nursing staff guide patients to understand the importance of self-care and the prevention and treatment of common health problems associated with CHB. They also promote patient self-care ability, an important component that is lacking in routine nursing. Furthermore, providing effective relief from negative emotions encourages patients to actively cooperate with treatment and related auxiliary interventions, accept guidance and transmission of nursing knowledge; it also enhances patient understanding of the disease and nursing measures, indirectly improving self-care abilities[24,25].

Some limitations should be noted. First, this was a single-center study; therefore, the application of these findings to those in different centers needs to be approached with caution and the results need to be corroborated in future studies. Second, this was a retrospective study, and the data may be subject to selection, information, and confounding biases. Therefore, prospective randomized controlled studies are required to obtain more accurate clinical data and generate more robust evidence.

CONCLUSION

The combination of ACT and ECBE in patients with CHB can improve psychological flexibility and sleep quality, alleviate negative emotions, and improve self-care abilities.

ARTICLE HIGHLIGHTS

Research background

Chronic hepatitis B (CHB) is an infectious, progressive disease. Patients experience a heavy psychological burden and severe insomnia symptoms.

Research motivation

Patients with CHB urgently require effective nursing interventions to alleviate mental flexibility, negative emotions, and sleep quality problems.

Research objectives

To analyze the effects of acceptance and commitment therapy (ACT) combined with enabling cognitive-behavioral education (ECBE) on mental flexibility, negative emotions, and sleep quality in CHB patients.

Research methods

We retrospectively analyzed the clinical data of 129 patients with CHB and observed changes and differences in Acceptance and Action Questionnaire-2nd edition (AAQ-II), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), and Exercise of Self-Case Agency Scale (ESCA) scores after routine nursing and ACT combined with ECBE intervention.

Research results

Compared to patients receiving conventional care, the AAQ-II, SAS, SDS, and PSQI scores in patients receiving ACT combined with ECBE were lower and ESCA scores were higher.

Research conclusions

ACT combined with ECBE is effective for CHB patients in China and overcomes the problem of nursing defects in CHB.

Research perspectives

We observed the mental flexibility, negative emotions, and sleep quality of patients with CHB according to two different nursing interventions: routine nursing and ACT combined with ECBE.

FOOTNOTES

Author contributions: Zheng Y designed and performed the study and wrote the paper; Xia CX designed the study and supervised the report; Wang XW designed the study and contributed to the analysis.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of The First People's Hospital of Wenling [Approval No. KY-2023-1032-01].

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ORIGINAL ARTICLE

Retrospective Study

Construction and validation of a personalized prediction model for postpartum anxiety in pregnant women with preeclampsia

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Abstract

BACKGROUND

Preeclampsia is a pregnancy-specific multi-system disease with multi-factor and multi-mechanism characteristics. The cure for preeclampsia is to terminate the pregnancy and deliver the placenta. However, it will reduce the perinatal survival rate, prolong the pregnancy cycle, and increase the incidence of maternal complications. With relaxation of the birth policy, the number of elderly pregnant women has increased significantly, and the prevalence rate of preeclampsia has increased. Inappropriate treatment can seriously affect the normal postpartum life of pregnant women. Studies have shown that postpartum anxiety in women with preeclampsia can affect physical and mental health, as well as infant growth and development.

AIM

To analyze the factors influencing preeclampsia in pregnant women complicated with postpartum anxiety, and to construct a personalized predictive model.

METHODS

We retrospectively studied 528 pregnant women with preeclampsia who delivered in Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine between January 2018 and December 2021. Their basic data were collected, and various physiological and biochemical indicators were obtained by laboratory examination. The self-rating anxiety scale was used to determine whether the women had postpartum anxiety 42 d after delivery. The independent factors influ-encing postpartum anxiety in early pregnant women with eclampsia were analyzed with multifactor logistic regression and a predictive model was constructed. The Hosmer-Lemeshow test and receiver operating characteristic (ROC) curve

were used to evaluate the calibration and discrimination of the predictive model. Eighty pregnant women with preeclampsia admitted to our hospital from January 2022 to May 2022 were retrospectively selected to verify the prediction model.

RESULTS

We excluded 46 of the 528 pregnant women with preeclampsia because of loss to follow-up and adverse outcomes. A total of 482 cases completed the assessment of postpartum anxiety 42 d after delivery, and 126 (26.14%) had postpartum anxiety. Bad marital relationship, gender discrimination in family members, hematocrit (Hct), estradiol (E2) hormone and interleukin (IL)-6 were independent risk factors for postpartum anxiety in pregnant women with preeclampsia ($P < 0.05$). Prediction model: Logit (P) = 0.880 × marital relationship + 0.870 × gender discrimination of family members + 0.130 × Hct - 0.044 × E2 + 0.286 × IL-6 - 21.420. The area under the ROC curve of the model was 0.943 (95% confidence interval: 0.919-0.966). The threshold of the model was -1.507 according to the maximum Youden index (0.757), the corresponding sensitivity was 84.90%, and the specificity was 90.70%. Hosmer-Lemeshow $\chi^2 = 5.900$, $P = 0.658$. The sensitivity, specificity and accuracy of the model were 81.82%, 84.48% and 83.75%, respectively.

CONCLUSION

Poor marital relationship, family gender discrimination, Hct, IL-6 and E2 are the influencing factors of postpartum anxiety in preeclampsia women. The constructed prediction model has high sensitivity and specificity.

Key Words: Preeclampsia; Postpartum anxiety; Risk factors; Predictive model

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Core Tip: Preeclampsia is a progressive multisystem disease during pregnancy, characterized by new hypertension and proteinuria after 20 wk of pregnancy, and the condition develops continuously, which has a serious effect on the health of the mother and child. We analyzed the biochemical indicators of 528 pregnant women with preeclampsia and the independent factors influencing postpartum anxiety, and constructed a predictive model, with high clinical value.

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INTRODUCTION

The incidence of preeclampsia can reach 8%[1], and studies have found that women with preeclampsia are more likely to suffer from postpartum anxiety[2-4], with an incidence of up to 20%[5]. Postpartum anxiety can aggravate maternal comorbidities, resulting in poor treatment compliance. Postpartum anxiety has short- or long-term adverse effects on maternal physical and mental health, as well as infant growth and development, and may lead to adverse events such as maternal drug abuse, suicide, and even infant injury[6,7]. Therefore, if we can predict the risk of postpartum anxiety in women with preeclampsia, targeted management and early intervention could avoid postpartum anxiety or improve postpartum psychological status. Current research focuses on the pregnancy outcome of women with preeclampsia, and few studies involve postpartum anxiety. In this study, we retrospectively studied 528 pregnant women with preeclampsia who delivered at our hospital between January 1, 2018 and December 31, 2021. The risk factors for preeclampsia in pregnant women complicated with postpartum anxiety were analyzed, and a predictive model was constructed to provide clinicians with an effective and practical risk assessment tool.

MATERIALS AND METHODS

General data

A total of 528 pregnant women with preeclampsia who delivered at Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine Jianka between January 2018 and December 2021 were retrospectively selected. Inclusion criteria were: (1) Pre-eclampsia was diagnosed according to the relevant standards of obstetrics and gynecology[8]; (2) Conception occurred naturally, the fetus was normal, and the pregnancy was singleton; (3) No cognitive impairment or history of mental illness, and normal communication; and (4) Age > 18 years and living in the local area. Exclusion criteria were: (1) Prenatal anxiety; (2) Medical history of encephalopathy; (3) Severe heart, liver, kidney and other organ diseases; (4) Concurrent diseases of the immune system, nervous system, severe cardiovascular disease and malignant

tumors; (5) Adverse pregnancy outcomes (including arrhythmia, fetal growth restriction, intrauterine fetal death, neonatal death, severe neonatal asphyxia, neonatal defects and serious postpartum complications); and (6) Patients who had to withdraw from the study due to an emergency.

The predictive model was clinically verified by retrospectively selecting 80 pregnant women with preeclampsia who met the above criteria in Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine between January and May 2022. Sample size calculation: (1) According to references, preeclampsia and the incidence of postpartum anxiety at about 20%, this study is expected to end in the multi-factor regression model analysis of 10 variables, according to the average number of events per predictor variable (EPV) sample size calculation, take EPV = 10, sample size = into variables × EPV/incidence rate = 10 × 10/20% = 500 cases, according to the inclusion and exclusion criteria and considering adverse outcomes, the sample size was 528; and (2) The sample size of the external validation was generally 1/4 to 1/2 of the modeling set, and the sample size = 1/4 of the modeling set, 120 cases (482/4) should be included. However, due to the influence of the external environment such as the epidemic situation and the actual situation of our hospital, 80 cases of preeclampsia pregnant women were finally included.

Data collection

General information: Age, educational level and occupation of pregnant women; occupation and educational level of spouse; family economic status; emotional status of husband and wife (self-rated as good or bad); whether pregnancy was planned; whether there was experience of raising children; whether there was gender discrimination on the part of oneself or family members (expecting to have male or female baby); whether there was regular maternity examination; and history of adverse pregnancy outcomes. Laboratory indicators included: Routine blood tests [including hematocrit (Hct), hemoglobin, and platelet count]; estrogen [including estradiol (E2)]; liver function (including alanine aminotransferase and aspartate aminotransferase); renal function (including creatinine and urea nitrogen); coagulation indicators (including fibrinogen and prothrombin time); and other biochemical indicators [including triglycerides and interleukin (IL)-6].

Postpartum anxiety criteria

The self-rating anxiety scale (SAS) was used to determine whether the parturients who completed the study had postpartum anxiety at 42 d postpartum. The SAS consisted of 20 items, with each item scoring 1 (none or few), 2 (sometimes yes), 3 (most of the time yes), and 4 (most of the time yes). In accordance with the Chinese standard, SAS score ≥ 50 indicated the presence of postpartum anxiety; a score of 50-59 indicated mild anxiety, 60-69 moderate anxiety, and ≥ 70 severe anxiety.

Statistical analysis

The data obtained were processed by SPSS 27.0. Measurement data and numerical data were expressed as mean ± SD and percentage, respectively, using t and χ^2 tests, respectively. The independent factors influencing postpartum anxiety in pregnant women with preeclampsia were analyzed using multifactor logistic regression and a predictive model was constructed. The Hosmer-Lemeshow test and receiver operating characteristic (ROC) curve were used to evaluate the calibration and discrimination of the predictive model. $P < 0.05$ indicated a significant difference.

RESULTS

Comparison of baseline data of pregnant women with preeclampsia

We excluded 46 of 528 pregnant women with preeclampsia because of loss to follow-up and adverse outcomes, and 482 women completed the anxiety assessment 42 d after delivery. Among them, 126 women (26.14%) experienced postpartum anxiety. The analysis of baseline data of 482 pregnant women with preeclampsia showed that marital relationship, gender discrimination of family members, Hct, E2 and serum IL-6 levels were factors potentially influencing postpartum anxiety in pregnant women with preeclampsia ($P < 0.05$) (Table 1).

Multifactor logistics regression analysis of pregnant women with preeclampsia complicated with postpartum anxiety

The significant factors above were used as covariates marital relationship (0 = good, 1 = bad), gender discrimination among family members (0 = none, 1 = yes). Concurrent postpartum anxiety was used as the dependent variable (0 = none, 1 = yes), and multifactor logistic regression analysis was performed. Bad marital relationship, gender discrimination among family members, Hct, E2 and IL-6 were independent risk factors for postpartum anxiety in pregnant women with preeclampsia ($P < 0.05$) (Table 2).

Construction and validation of predictive model for pregnant women with preeclampsia complicated with postpartum anxiety

According to the multivariate logistic regression model, a predictive model of postpartum anxiety in pregnant women with preeclampsia was constructed: Logit(P) = 0.880 × conjugal affection + 0.871 × gender discrimination in family members + 0.130 × Hct - 0.044 × E2 + 0.286 × IL-6 - 21.420. The ROC curve was drawn to evaluate the discrimination of the predictive model. The area under the ROC curve was 0.943 (95% confidence interval: 0.919-0.966). The threshold of the model was -1.507 according to the most approximate maximum Youden index (0.757), and the corresponding sensitivity and specificity were 0.849 and 0.907, respectively (Figure 1). The goodness-of-fit test was used to evaluate the

Table 1 Comparison of baseline data of pregnant women with preeclampsia, *n* (%)

Variable	Postpartum anxiety (*n* = 126)	No postpartum anxiety (*n* = 356)	t/χ^2	*P* value
Age (mean ± SD)	31.80 ± 3.99	32.04 ± 4.09	0.491	0.624
Degree of education			1.853	0.396
Junior high school and below	31 (24.60)	70 (19.66)		
Senior high school (technical secondary school)	61 (48.41)	172 (48.31)		
College (higher vocational) or above	34 (26.98)	114 (32.02)		
Occupation			5.433	0.143
Unemployed	25 (19.84)	50 (14.04)		
Workers and peasants	43 (34.13)	150 (42.13)		
Public official	19 (15.08)	37 (10.39)		
Other	39 (30.95)	119 (33.43)		
Per capita monthly household income			4.491	0.106
< 2500 RMB yuan	22 (17.46)	68 (19.10)		
2500-5000 RMB yuan	65 (51.59)	146 (41.01)		
> 5000 RMB yuan	39 (30.95)	142 (39.89)		
Spousal occupation			3.390	0.335
Unemployed	13 (10.32)	20 (5.62)		
Workers and peasants	59 (46.83)	181 (50.83)		
Public official	21 (16.67)	57 (16.01)		
Other	33 (26.19)	98 (27.53)		
Education level of spouse			3.994	0.136
Junior high school and below	19 (15.08)	40 (11.24)		
Senior high school (technical secondary school)	58 (46.03)	200 (56.18)		
College (higher vocational) or above	49 (38.89)	116 (32.58)		
Marital relationship			37.665	< 0.001
Good	39 (30.95)	223 (62.64)		
Bad	87 (69.05)	133 (37.36)		
Whether it was a planned pregnancy			1.338	0.247
Yes	80 (63.49)	246 (69.10)		
No	46 (36.51)	110 (30.90)		
Have any experience raising children			0.253	0.615
Yes	38 (30.16)	99 (27.81)		
No	88 (69.84)	257 (72.19)		
Whether the pregnant woman herself has gender discrimination			0.471	0.493
Yes	28 (22.22)	90 (25.28)		
No	98 (77.78)	266 (74.72)		
Gender discrimination among family members			24.318	< 0.001
Yes	86 (68.25)	152 (42.70)		
No	40 (31.75)	204 (57.30)		
Whether regular birth inspection			1.846	0.174

Yes	84 (66.67)	260 (73.03)		
No	42 (33.33)	96 (26.97)		
History of adverse pregnancy outcomes			0.256	0.613
Yes	30 (23.81)	77 (21.63)		
No	96 (76.19)	279 (78.37)		
Systolic blood pressure (mean ± SD, mmHg)	149.57 ± 7.3	149.50 ± 8.08	-0.087	0.930
Diastolic blood pressure (mean ± SD, mmHg)	100.37 ± 5.97	99.62 ± 6.70	-1.113	0.266
Hemoglobin (mean ± SD, g/L)	108.47 ± 25.25	112.90 ± 30.02	1.700	0.090
Hct (mean ± SD, %)	63.16 ± 8.49	47.23 ± 6.18	-22.421	< 0.001
Platelets (mean ± SD, × 10^9/L)	137.72 ± 33.06	141.53 ± 32.63	1.121	0.263
Fibrinogen (mean ± SD, g/L)	4.38 ± 1.03	4.59 ± 1.11	1.749	0.081
Prothrombin time (mean ± SD, s)	10.96 ± 3.04	11.27 ± 3.01	0.991	0.322
Creatinine (mean ± SD, mmol/L)	60.64 ± 18.51	58.91 ± 16.86	-0.963	0.336
Urea nitrogen (mean ± SD, mmol/L)	4.16 ± 1.09	3.99 ± 0.97	-1.597	0.111
Alanine transaminase (mean ± SD, U/L)	27.21 ± 7.12	26.70 ± 7.23	-0.685	0.494
Aspartate aminotransferase (mean ± SD, U/L)	29.85 ± 9.05	28.82 ± 9.31	-1.071	0.285
Triglyceride (mean ± SD, mmol/L)	4.67 ± 1.08	4.18 ± 1.09	-1.657	0.098
Estradiol (mean ± SD, pg/mL)	50.23 ± 15.00	57.97 ± 11.95	5.845	< 0.001
Interleukin-6 (mean ± SD, pg/mL)	56.39 ± 12.22	40.24 ± 10.12	-14.554	< 0.001

Hct: Hematocrit.

Table 2 Multifactor logistic regression analysis of postpartum anxiety in pregnant women with preeclampsia

Factor	*β*	Wald χ^2	*P* value	OR (95%CI)
bad marital relationship	0.880	4.594	0.032	2.412 (1.078-5.394)
Gender discrimination among family members	0.871	4.339	0.037	2.390 (1.053-5.425)
Hematocrit	0.130	35.391	< 0.001	1.139 (1.091-1.189)
Eastradiol	-0.044	8.039	0.005	0.957 (0.928-0.986)
Interleukin-6	0.286	64.504	< 0.001	1.331 (1.242-1.428)
Constant	-21.420	72.926	< 0.001	

OR: Odds ratio; CI: Confidence interval.

calibration of the predictive model, which showed Hosmer-Lemeshow χ^2 = 5.900, and P = 0.658 (Figure 2).

Clinical verification of predictive model for pregnant women with preeclampsia complicated with postpartum anxiety

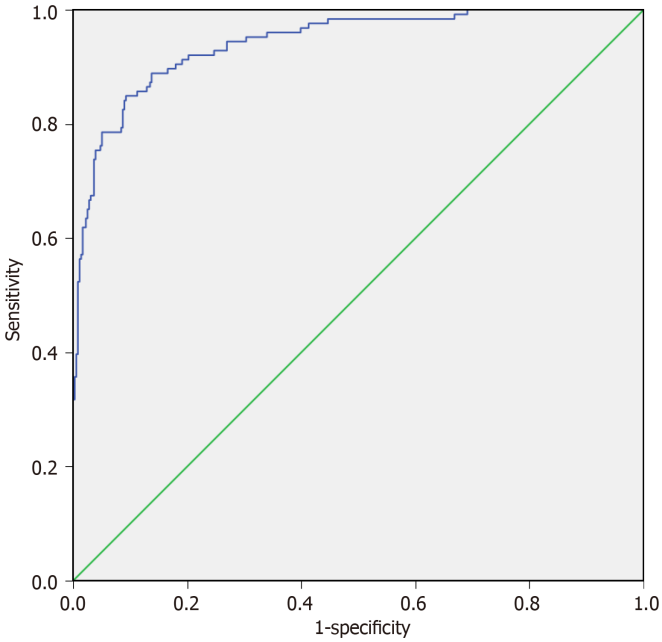
We retrospectively selected 80 pregnant women with preeclampsia in our hospital between January and May 2022 to clinically verify the predictive model. The sensitivity was 81.82%, specificity 84.48%, and accuracy 83.75% (Table 3).

DISCUSSION

The results of this study showed that serum transaminase levels, blood pressure, platelet levels, and coagulation indicators in pregnant women with preeclampsia with postpartum anxiety did not differ significantly from those in women without postpartum, which was consistent with previous studies[4]. We found that bad marital relationship, gender discrimination among family members, Hct, IL-6 and E2 were all independent factors influencing postpartum anxiety in pregnant women with preeclampsia. The care and support of husbands play a key role in improving the psychological status of pregnant women[9,10]. Therefore, strengthening the health education of the spouses of pregnant and lying-in

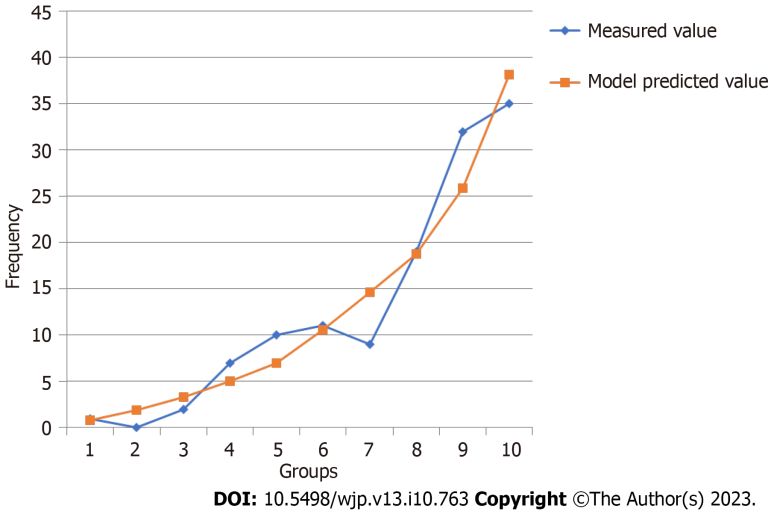
Table 3 Clinical validation of the predictive model

Postpartum anxiety	Models predict postpartum anxiety		Total
	Yes	No	
Yes	18	4	22
No	9	49	58
Total	27	53	80



DOI: 10.5498/wjp.v13.i10.763 **Copyright** ©The Author(s) 2023.

Figure 1 Receiver operating characteristic curve analysis of the predictive model for postpartum anxiety in preeclampsia.



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Figure 2 Goodness of fit test of a predictive model for postpartum anxiety in women with preeclampsia.

women and guiding them to attach importance to psychological care and support are important to reduce the risk of postpartum anxiety. The feudal thought of "son preference" is deeply rooted in China. Family members and even the pregnant women themselves care about the gender of the newborn[11]. When pregnant women with preeclampsia excessively consider the views of family members on the gender of their newborn, it can easily exert psychological pressure, leading to postpartum anxiety. Therefore, for pregnant women with preeclampsia, health education should be strengthened during prenatal examination, the idea of gender equality should be advocated, and possible gender discrim-

ination should be corrected in time to reduce the risk of postpartum anxiety of pregnant women.

There is a biological basis for postpartum anxiety in pregnant women with preeclampsia. Postpartum estrogen deficiency is an important reason for the significantly increased incidence of mental illness at 30 d postpartum[12], and E2 level is negatively correlated with the severity of female anxiety[13], which is similar to our study. The possible causes are that E2 can play an antianxiety role by improving the binding rate of serotonin reuptake transporter and the reuptake capacity of cells for serotonin. However, postpartum estrogen secretion from the uterus is stopped, the recovery of ovarian estrogen secretion function is slow, and the level of E2 is low, thus the antianxiety effect is weakened. If the level of E2 is low in pregnant women with preeclampsia, it may further decrease the level of postpartum estrogen, so anxiety is more likely to occur[14,15]. Ramiro-Cortijo *et al*[16] confirmed that the Hct in patients with preeclampsia was significantly higher than that of healthy people, and increased with aggravation of preeclampsia. Noori *et al*[17] showed that the prenatal Hct accurately predicted severity of depression and anxiety 6 wk after delivery. The results of this study showed that Hct was an independent factor influencing postpartum anxiety in pregnant women with preeclampsia, which was consistent with the above conclusions. Pregnant women with preeclampsia usually have overactivation of inflammation and immunity, and a large number of inflammatory factors are released into the blood, resulting in increased serum IL-6 level, which is positively correlated with the severity of preeclampsia[18]. Immune activation caused by inflammatory factors can lead to dysfunction of the neuroendocrine and immune systems[19,20]. Therefore, elevated serum IL-6 levels may cause postpartum anxiety in women with preeclampsia. Therefore, clinical attention should be paid to patients with abnormal indicators, and follow-up observation should be strengthened, or appropriate treatment should be given to adjust the level of related indicators.

In this study, a risk predictive model for pregnant women with preeclampsia complicated with postpartum anxiety was constructed based on the above independent influencing factors (bad marital relationship, gender discrimination of family members, Hct, IL-6 and E2). The ROC curve analysis results showed that the predictive model had good discrimination, and the goodness-of-fit test showed that the model had good calibration. The prospective clinical validation showed that the model had high sensitivity (81.82%), specificity (84.48%) and accuracy (83.75%), indicating that the predictive model had clinical practicability. The model was simple to use and had high accuracy. However, the number of cases in the time period selected for clinical verification is small, and the results may have certain errors. In the future will be incorporated into various validation.

CONCLUSION

Bad marital relationship, gender discrimination of family members, Hct, IL-6 and E2 are independent factors influencing postpartum anxiety in pregnant women with preeclampsia. The predictive model established based on these factors has high sensitivity, specificity and accuracy, strong operability, and high clinical value. However, this study was a single-center study, the clinical validation of the model was only conducted in our hospital, and the sample size was insufficient, so the results were inevitably biased. In the future, multi-center research and multi-center clinical verification will be carried out, and multi-factor, multi-sample and multi-time span will be adopted to explore, so as to enhance the reliability of the research results.

ARTICLE HIGHLIGHTS

Research background

Relaxation of the maternity policy has resulted in an increase in the number of elderly pregnant and lying-in women, and the prevalence of preeclampsia. Preeclampsia can lead to organ damage and system dysfunction.

Research motivation

To explore the factors influencing postpartum anxiety in pregnant women with preeclampsia and construct a predictive model, to provide an effective and practical risk assessment tool for clinical practice.

Research objectives

The object of this study is to explore the factors influencing postpartum anxiety in pregnant women with preeclampsia and construct a personalized model for predicting postpartum anxiety, to provide a reference for clinical trials.

Research methods

We retrospectively analyzed 528 pregnant women with preeclampsia who delivered in our hospital between 2018 and 2021. Various physiological and biochemical indicators were obtained through laboratory tests. Multivariate logistic regression, receiver operating characteristic curve, Hosmer-Lemeshow and other methods were used to analyze the factors influencing postpartum anxiety in pregnant women with preeclampsia and to construct a predictive model.

Research results

A total of 126 pregnant women with preeclampsia experienced postpartum anxiety. Bad marital relationship, gender discrimination among family members, hematocrit, estradiol hormone and interleukin-6 were independent risk factors

for postpartum anxiety in pregnant women with preeclampsia, and the predictive model constructed based on these factors had high accuracy.

Research conclusions

We analyzed the factors influencing postpartum anxiety in pregnant women with preeclampsia and constructed a predictive model with high sensitivity and accuracy, which provided a reference value for clinical practice.

Research perspectives

Firstly, multi-sample, multi-factor, multi-center and multi-time span clinical studies will be carried out in the future to enhance the reliability of the research results. In addition, different models were constructed for clinical application in pregnant women with preeclampsia and postpartum anxiety.

FOOTNOTES

Author contributions: Lin LJ and Chen S designed the study and wrote the paper; Zhou HX participated in the analysis; Ye ZY and Zhang Q provided clinical advice.

Institutional review board statement: The study was reviewed and approved by the Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, No. 20230424085200033546 5.

Informed consent statement: All patients have signed informed consent forms.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The dataset used for this study can be obtained from the corresponding author.

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ORIGINAL ARTICLE

Observational Study

Depression among medical students in Tunisia: Prevalence and associated factors

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Abstract

BACKGROUND

Medical school is known for its lengthy process, which is both physically and emotionally draining. Students' mental balance would shrink as they progress in their medical training. A systematic review and meta-analysis reported that the prevalence of depressive symptoms among medical students remained relatively constant at 27.2%.

AIM

To assess the prevalence of depressive symptoms among Tunisian medical students and evaluate its associated factors.

METHODS

This is a descriptive cross-sectional study that was carried out in the second semester of the academic year 2017/2018, between April 2018 and July 2018 among 1138 medical students. Data were collected using a socio-demographic questionnaire and the Beck Depression Inventory-II (BDI-II).

RESULTS

Sixty-four percent (n = 728) of the participants had depressive symptoms, of which 266 (23.4%) met the criteria for mild, 271 (23.8%) for moderate, and 191 (16.8%) for severe depressive symptoms. Female gender, low socio-economic level, smoking habits and history of mental disorder, performing leisure and physical activities, satisfaction toward a career choice, and happiness perception were the main prognostic factors for depression among medical students. Although academic grades may not be considered a prognostic factor, final-year

students appeared to be less depressive than their colleagues.

CONCLUSION

These findings give insight into mental health issues and comorbidities among Tunisian medical students. It is a hopeful request for decision-makers and academic authorities to set serious measures and draw effective interventions to minimize the currency of psychological distress among this subpopulation.

Key Words: Depression; Psychiatry; Medical students; Mental health; Beck Depression Inventory; Tunisia

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Core Tip: This study aimed to assess the prevalence of depressive symptoms among Tunisian medical students and evaluate its associated factors. This is a descriptive cross-sectional study that was carried out in the second semester of the academic year 2017/2018, between April 2018 and July 2018 among 1138 medical students. Sixty four percent (n = 728) of the participants had depressive symptoms, of which 266 (23.4%) met the criteria for mild, 271 (23.8%) for moderate, and 191 (16.8%) for severe depressive symptoms. Female gender, low socio-economic level, smoking habits and history of mental disorder, performing leisure and physical activities, satisfaction toward career choice, and happiness perception were the main prognostic factors for depression among medical students. Although academic grade may not be considered as a prognostic factor, final year students appeared to be less depressive than their colleagues.

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INTRODUCTION

The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017), conducted between 1990 and 2017 in 195 countries and territories, concluded that more than 264 million people of all ages were depressed[1].

Depression can be long-lasting or recurrent, and standing still impairs an individual's ability to function in his daily life[2].

Psychological distress among university students has witnessed a considerable rise, becoming a concern for public health authorities around the globe. And among university students, medical students are particularly more vulnerable to psychological distress and morbidity since medical education is reputed for its long process and it is physically and emotionally consuming[3,4].

Rotenstein *et al*[5] reported in a systematic review and meta-analysis conducted in 2016 that between 1982 and 2015, depressive symptom prevalence remained relatively constant at 27.2% for medical students with no significant difference between preclinical and clinical students.

Even though it is crucial for an educational institution to assess the mental status of its students, only a few Tunisian studies surveyed the currency of depression among medical students.

Within this framework, this study aimed to assess the prevalence of depressive symptoms among medical students in Tunisia and to evaluate its associated factors.

MATERIALS AND METHODS

Study design and participants

The present study is a descriptive cross-sectional study that was carried out in the second semester of the academic year 2017/2018, between April 2018 and July 2018 (away from exams). We recruited students from the four medical faculties in Tunisia [Faculty of Medicine of Monastir (FMM), Sousse, Tunis, and Sfax].

The minimal sample size required for the study was 322694. It was calculated using the formula: $n = \mu\alpha 2\ p\ (1\text{-}p)/\delta 2$, where "μα" is the one-sided magnitude of the confidence level (μα = 1.96) and "p" is the expected proportion of the outcome of interest with an assumption of 30% depression among medical students.

Only enrolled medical students from the first year to the fifth year were invited to complete an online survey as a main tool of the study.

To retrieve an adequate sample for the present study, all candidates were invited to complete an anonymous nationwide web-based questionnaire *via* their student delegate who published the questionnaire in their Facebook group, mentioning the purpose of the study and assuring the confidentiality and anonymity of each answer. The questionnaire was sent with a description of the study. Every person could only answer the questionnaire once.

As the response rate is the number of completed and sent survey responses divided by the number of people who viewed the survey, the present study response rate was measured to be 16.45%, considering students who reached the link and viewed the survey content (Figure 1).

Study instruments

The self-report questionnaire employed in the French language (the second language and official language for medical studies in Tunisia) took approximately 15 min to answer and collected data on.

Students' general characteristics: It consists of personal (age, gender, origin, personal medical history, tobacco use, alcoholism, marital status, self-assessment of their financial status, and current residence) and academic characteristics: Faculty, academic level, satisfaction toward career choice, and dropping out thoughts, leisure and sporting activities, participation in a stress management workshop, and a precedent visit to a psychiatrist/psychologist.

Beck Depression Inventory-II (BDI-II): It is a self-administrated tool, used to screen for the presence of depressive symptoms[6,7]. The BDI-II timeframe extends for 2 wk to correspond with the DSM-IV criteria for diagnosing depressive disorders and includes items measuring cognitive, affective, somatic, and vegetative symptoms of depression. With a sensitivity of 87% and specificity of 79%, the BDI-II was validated using adult and adolescent psychiatric outpatients.

Each participant is asked to answer 21 items rated on a 4-point Linkert scale indicating the degree of severity from 0 (not at all) to 3 (extreme form of each symptom). Cumulative score is calculated. The provisional diagnosis of depression is made if the BDI-II score is greater than 13 and the presence of severe depressive symptoms if the score is greater than or equal to 29. The severity of depression was classified into three categories: Mild, moderate, and severe depression[7,8].

Statistical analysis

The data collected were keyed into Excel for Windows and statistical analyses were carried out using the software package SPSS version 24 (SPSS Inc.). Descriptive analysis (frequencies, prevalence, mean, and standard deviation) was applied to evaluate the characteristics of the samples. The Chi-square (χ^2) test was carried out to compare the prevalence of depression between different groups, while the Student's *t*-test was used to analyze quantitative data (age) with the presence of depression. Variables whose *P* value was < 0.2 were entered as independent variables in regression analysis. The 95% confidence intervals (95%CI) were calculated for prevalence rates. Binary logistic regression models were used to show the predictive model of BDI based on the values of the independent variables (predictors). The level of significance was set at $P < 0.05$.

Ethical considerations

We explained the purpose of the study to all participants. The confidentiality and anonymity of each answer were guaranteed. A completed questionnaire was considered as consent to participate in the study. The present study was approved by the ethics committee of the FMM (No. 3067).

RESULTS

Description of general characteristics

The sample consisted of 1138 medical students, including 888 (78%) females and 250 (22%) males, with ages ranging from 18 to 37 years (mean, 22.0 years ± 2.3 years). There were 423 students (37.2%) who were enrolled in the Faculty of Medicine of Tunis (FMT), while 304 (26.7%), 248 (21.8%), and 163 (14.3%) were registered, respectively, in the FMM, Sousse (FMS) and Sfax (FMSF). Of the sample, there were 448 pre-clinical students (Year 1 and Year 2) (39.3%) and 690 clinical students (Year 3, Year 4, and Year 5) (60.6%).

Based on their financial status self-assessment, most of the students (921, 80.9%) were at a moderate socio-economic level while 146 (12.8%) were at a high level and 71 (6.2%) were at a low level. Fourteen percent of the participants were smokers and 16% revealed drinking habits. Almost 70% of the sample did not practice either leisure or physical activities. Only 158 (13.9%) had participated in a stress management workshop and 228 (20%) had sought psychiatric help.

Half of the sample were unsatisfied with their career choice and have thought, at least once, of dropping out of medical studies. Sixty-one percent of participants (699) admitted feeling unhappy. More personal and academically related details are illustrated in Table 1.

Depressive symptoms

The BDI-II total scores of participants ranged from 0 to 63 with a mean score of 18.73 ± 10.60 as shown in Table 2. Sixty-four percent (n = 728) of the participants had depressive symptoms, of which 266 (23.4%) met the criteria for mild, 271 (23.8%) for moderate, and 191 (16.8%) for severe depressive symptoms. Among 728 depressive students, only 177 (24.3%) had sought psychiatric help.

Students' general characteristics as determinants of depression

Personal characteristics: Female students were more depressed than males. Neither students' residency nor marital status showed a significant effect on depressive symptoms. Depression was more prevalent among smokers and students with low socio-economic levels.

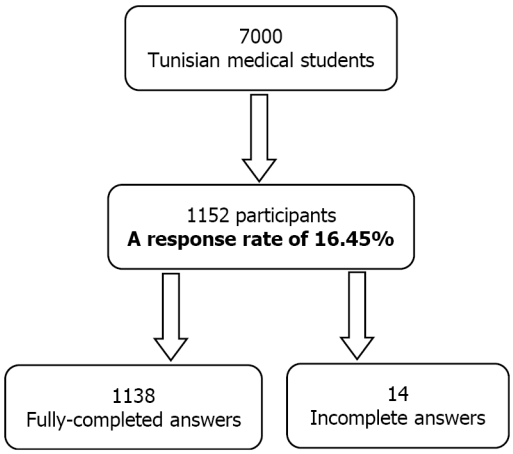
Table 1 Characteristics of study participants (*n* = 1138) (university year 2017/2018), *n* (%)

Characteristic		mean ± SD
Age, yr		22 (2.347) (min 18, max 37)
Gender	Female	888 (78)
	Male	250 (22)
Faculty	Monastir	304 (26.7)
	Sousse	248 (21.8)
	Sfax	163 (14.3)
	Tunis	423 (37.2)
Grade	Year 1	252 (22.1)
	Year 2	196 (17.2)
	Year 3	198 (17.4)
	Year 4	171 (15)
	Year 5	321 (28.2)
Marital status	Single	837 (73.6)
	Engaged	269 (23.6)
	Married	29 (2.5)
	Divorced	3 (0.3)
	Alone	193 (17)
	With friends/roommates	220 (19.3)
	Academic residency	127 (11.2)
	Family home	598 (52.5)
Socio-economic level	Low	71 (6.2)
	Moderate	921 (80.9)
	High	146 (12.8)
Children	Yes	23 (2)
	No	1115 (98)
History of medical illness	Yes	173 (15.2)
	No	965 (84.8)
History of mental illness	Yes	79 (6.9)
	No	1059 (93.1)
Leisure activities	Yes	349 (30.7)
	No	789 (69.3)
Physical activities	Yes	322 (28.3)
	No	816 (71.7)
Smoking habits	Yes	160 (14.1)
	No	978 (85.9)
Drinking habits	Yes	183 (16.1)
	No	955 (83.9)
Are you satisfied with your career choice?	Yes	619 (54.4)
	No	519 (45.6)
Have you ever thought of dropping out of medical studies?	Yes	664 (58.3)
	No	474 (41.7)

Stress management training	Yes	158 (13.9)
	No	980 (86.1)
Have you ever visited a psychiatrist?	Yes	228 (20)
	No	910 (80)
Why not?	No answer	261 (22.9)
	I feel fine. I don't need it	392 (34.4)
	I need it, but I am always busy	366 (23.2)
	I need it, but my circle of friends/family discouraged me	119 (10.5)
Are you happy?	Yes	439 (38.6)
	No	699 (61.4)

Table 2 Prevalence of depression among study participants (*n* = 1138)

BDI-II total score, mean ± SD		**Min 0, max 63, 18.730 (10.654)**
Depression level	Absence of depression	410 (36%)
	Low	266 (23.4%)
	Moderate	271 (23.8%)
	Severe	191 (16.8%)



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Figure 1 Flowchart of the study.

Depressive symptoms were associated with age ($P = 0.048$; the age difference was not meaningful), gender ($P = 0.038$), socio-economic level ($P < 10^{-3}$), history of medical illness ($P = 0.034$), history of mental illness ($P < 10^{-3}$), and smoking habits ($P = 0.025$).

Academic characteristics: With 70% depressed students, Sousse Faculty of Medicine was ranked as the most depressed faculty. There was no difference between pre-clinical and clinical students. The lack of leisure and physical activities was significantly associated with the presence of depressive symptoms.

The presence of depression was associated with faculty ($P = 0.042$), leisure activities ($P < 10^{-3}$), physical activities ($P < 10^{-3}$), satisfaction toward career choices ($P < 10^{-3}$), dropping out thoughts ($P < 10^{-3}$), a precedent visit of a psychiatrist/psychologist ($P < 10^{-3}$), and happiness perception ($P < 10^{-3}$). Different correlations are illustrated in Table 3.

Association between depressive symptoms and sample characteristics: Regression analysis

Female gender, low socio-economic level, smoking habits, and history of mental disorders were identified to be the main prognostic factors for depression among medical students (Table 4).

Although academic grade and participation in a stress management workshop did not show a significant correlation in the univariate analysis, we added these two variables in the regression analysis as they were mentioned in the literature. Academic grade may not be considered a prognostic factor. However, as detailed in Table 4, final-year students seemed

Table 3 Association between characteristics of participants and symptoms of depression, *n* (%)

Characteristic		D-	D+	*P* value
Age, yr, mean ± SD		21.820 (2.059)	22.100 (2.492)	0.048
Gender	Female	306 (34.5)	582 (65.5)	0.038
	Male	104 (41.6)	146 (58.4)	
Faculty	Monastir	124 (40.8)	180 (59.2)	0.042
	Sousse	73 (29.4)	175 (70.6)	
	Sfax	63 (38.7)	100 (61.3)	
	Tunis	150 (35.5)	273 (64.5)	
Grade	Year 1	91 (36.1)	161 (63.9)	0.57
	Year 2	72 (36.7)	124 (63.3)	
	Year 3	74 (37.4)	124 (62.6)	
	Year 4	52 (30.4)	119 (69.6)	
	Year 5	121 (37.7)	200 (62.3)	
Accomodation	Alone	63 (32.6)	130 (67.4)	0.597
	With friends/roommates	79 (35.9)	141 (64.1)	
	Academic residency	43 (33.9)	84 (66.1)	
	Family home	225 (37.6)	373 (62.4)	
Marital status	Single	301 (36)	536 (64.0)	0.786
	Engaged	100 (37.2)	169 (62.8)	
	Married	8 (27.6)	21 (72.4)	
	Divorced	1 (33.3)	2 (66.7)	0.149
Children	Yes	5 (21.7)	18 (78.3)	
	No	405 (36.3)	710 (63.7)	
Socio-economic level	Low	9 (12.7)	62 (87.3)	$< 10^{-3}$
	Moderate	330 (35.8)	591 (64.2)	
	High	71 (48.6)	75 (51.4)	
History of medical illness	Yes	50 (28.9)	123 (71.1)	0.034
	No	360 (37.3)	605 (62.7)	
History of mental illness	Yes	14 (17.7)	65 (82.3)	$< 10^{-3}$
	No	396 (37.4)	663 (62.6)	
Leisure activities	Yes	172 (49.3)	177 (50.7)	$< 10^{-3}$
	No	238 (30.2)	551 (69.8)	
Physical activities	Yes	145 (45)	177 (55)	$< 10^{-3}$
	No	265 (32.5)	551 (67.5)	
Smoking habits	Yes	45 (28.1)	115 (71.9)	0.025
	No	365 (37.3)	613 (62.7)	
Drinking habits	Yes	63 (34.4)	120 (65.6)	0.622
	No	347 (36.3)	608 (63.7)	
Are you satisfied with your career choice?	Yes	305 (49.3)	314 (50.7)	$< 10^{-3}$
	No	105 (20.2)	414 (79.8)	
Have you ever thought of dropping out of medical studies?	Yes	167 (25.2)	497 (74.8)	$< 10^{-3}$
	No	243 (51.3)	231 (48.7)	

Stress management training	Yes	49 (31.0)	109 (69.0)	0.157
	No	361 (36.8)	619 (63.2)	
Have you ever visited a psychiatrist?	Yes	51 (22.4)	177 (77.6)	$< 10^{-3}$
	No	359 (39.5)	551 (60.5)	
	No			
Are you happy?	Yes	289 (65.8)	150 (34.2)	$< 10^{-3}$
	No	121 (17.3)	578 (82.7)	

Table 4 Binary logistic regression analysis of association between the sample and depression symptoms

Characteristic		Exp (B)	95%CI	*P* value
Gender		1.544	1.135-2.099	0.006
Socio-economic level	High	1		
	Moderate	1.83	1.276-2.633	0.001
	Low	6.589	3.000-14.469	$< 10^{-3}$
History of mental illness		2.693	1.470-4.932	0.001
Smoking habits		1.669	1.123-2.481	0.011
Grade	Year 1	1		
	Year 2	0.991	0.653-1.504	0.966
	Year 3	0.796	0.523-1.213	0.288
	Year 4	0.918	0.584-1.444	0.711
	Year 5	0.667	0.456-0.974	0.036
Leisure activities		0.459	0.344-0.613	$< 10^{-3}$
Physical activities		0.679	0.505-0.914	0.011
Satisfaction toward career choice		0.238	0.179-0.316	$< 10^{-3}$
Stress management training		1.609	1.085-2.385	0.018
Happiness perception		0.143	0.107-0.193	$< 10^{-3}$

to be less depressed than their colleagues.

Performing leisure and physical activities, satisfaction toward a career choice, happiness perception, and participation in a stress management workshop were considered prognostic factors for depression among participants.

DISCUSSION

Prevalence of depression among students

Sixty-four percent (n = 728) of the participants had depressive symptoms. These results seem to be higher than the aggregate prevalence of 27.2% (range, 9.3%-55.9%) reported by Rotenstein *et al*[5] in their systematic review and meta-analysis that covered 195 studies in 47 different countries, involving 129123 medical students. In a medical education journal, a meta-analysis that concerned a total of 62728 medical students pooled across 77 studies was published in March 2016[9], which reported similar results (28%).

The magnitude of depression found in our study closely resembled the findings from some neighboring countries: Egypt 60.2%[10], Bahrain 65.6%[11], *etc*. Lower prevalence were found in India[12] (18%), Thailand[13] (12.6%), Germany [14] (10.3%), *etc*.

Nationally, the proportion of depressed medical students was higher than what was reported in a previous Tunisian study[15] that was conducted at the University of Sfax and showed that out of 80 medical students, 31% were depressed. Similar results were found in another study that included Tunisian medical residents (30.5%)[16]. Both studies used the same screening tool (Hospital Anxiety and Depression scale)[15,16].

This variation worldwide can be explained to be due to sample size and data collection tools. Besides, diversity in cultural, religious, and spiritual peculiarities[17] in addition to dissimilarity in the healthcare system might also elucidate the disparity of findings between countries.

Association between characteristics of participants and symptoms of depression

Female gender: Globally, there were controverted issues given the impact of gender on depression symptoms. The significant correlation of poor mental health with female students found in the current study is supported by previous studies in Sweden[18], Nepal[19], Australia[20], *etc*. In contrast, no difference in depression between genders was disclosed in previous studies in Tunisia[16], Greece[21], Ethiopia[22], *etc*. Furthermore, regression analysis yielded mixed findings with some considering female gender as a risk factor for depression: South Africa[23], Turkey[24], South Korea [25], *etc*. Studies took a multitude of tracks to elucidate why female students were more prone to depression than their male peers, and they suggested social stigma, gender inequity, and cultural constraints as the main reasons[9,26,27].

Financial status: Based on their financial status self-assessment, students at a low socioeconomic level were more likely to get depressed than their peers. These outcomes are in harmony with those run in neighboring and foreign countries[3,10, 14,25,28]. The impact of financial status on the occurrence of depression was documented in numerous studies among general populations[29-32]. A large four-year study (The PATH Through Life Survey) was conducted by Butterworth and colleagues in the city of Canberra and the surrounding regions in south-east Australia, and it included 6715 participants from different cohorts (1975-1979; 1956-1960; and 1937-1941). The study proclaimed that the lack of financial resources was strongly associated with depression[33,34].

Mental problems: Out of 1138 participants, 79 (6.9%) reported having a history of mental illness. These results seem to be akin to those found in other studies[26,35]. Nineteen Saudi Arabian medical students (out of 398) reported having a psychological illness. Eighty-four percent of them met the BDI criteria for depression. The chi-square test detected a significant correlation ($P < 0.001$) and multiple linear regression inferred that the presence of psychological problems makes students 1.435 times more likely to get depressed [$P = 0.03$, exp(B) 4.200, 95%CI: 1.150-15.338][35]. These findings are congruous with those reported earlier by Asal *et al*[36], Pagnin *et al*[37], and Pillay *et al*[38], who found that depressive and anxiety features were related to students' history of poor mental health[36-38].

Smoking, drinking, and substance use: Out of 1138 participants, 160 (14.1%) had smoking habits while 183 (16.1%) had drinking habits. Smokers (115, 71.9%) and drinkers (120, 65.6%) met the BDI-II criteria for depression. The regression analysis considered smoking as a risk factor for depression. Many studies have looked for the link between substance use and the occurrence of depression[39]. On the other hand, Palestinian and Saudi Arabian studies that explored the impact of smoking only (but not drinking for cultural limitations) found no significant correlation with depression ($P = 0.08$)[26, 35]. Moreover, O. Coskun and colleagues[24] perceived no significant relationship between alcohol and the magnitude of depression. Correspondingly, studies among Ethiopian, Nepali, and Australian medical students found, also, no significant link between substance use and the development of depression[19,20,22]. Strikingly, a similar study was performed in the Netherlands. Authors noticed that first-year students who had drinking habits tended to be more balanced in their mental wellness than non-drinking students. Hence, drinking seems to be a coping tool wielded to ease the pressure but also to inflate social interactions and activities[40,41]. Even though drinking can be regarded as a relief from stress or a coping strategy, immoderate drinking may ruin liver and pancreas functioning, alter the cardiovascular system, and lead to tumoral issues as well as numerous psychiatric disorders[41-44].

Association between academic characteristics of participants and depression symptoms

Physical activities: Almost 70% of the sample did not practice any physical activity. Among them, 551 (67.5%) met the BDI-II criteria for depression. The regression analysis considered physical activity as a protective factor against depression[45].

A tiny number of studies had explored physical behavior among medical students. Abdelwahed and colleagues, for instance, observed that 210 out of 442 were performing physical activity at least three times a week. Yet, statistical analysis did not show any significant correlation between physical activity and depression ($P = 0.647$), anxiety ($P = 0.78$), or stress ($P = 0.76$)[10].

Worldwide, the impact of physical exercises was exemplified in numerous studies. A systematic review on the effects of physical activity on brain structure and function in youth related that physical activity can redesign white matter integrity and arousal of regions key to cognitive tasks[46]. Identically, Rebar and colleagues performed a meta-analysis of the impact of physical activity on depression and anxiety among the non-clinical population[47]. Authors concluded that physical activity was shown to decrease depression by a medium effect [standardized mean difference (SMD) = -0.50; 95%CI: -0.93 to -0.06] and anxiety by a small effect (SMD = -0.38; 95%CI: -0.66 to -0.11)[47].

Leisure activities and extracurricular involvement: More than half of the participants (69.3%) were not performing any leisure activity. Fifty hundred and fifty-one (69.8%) among them were found depressed. Statistical analysis proved a significant association between spare time ventures and the occurrence of depression: The odds of developing depression was reduced to half among socially active participants. These findings seem in line with a Nepalian study where 34% of students (221/651) were involved in extracurricular activities. While those who answered "Always" and "Often" as the frequency of their extra activities were 28.6% and 21.7% depressed, respectively, those who answered "Rarely" and "Never" were 42.4% and 41.7% depressed, respectively. Even though a strong correlation ($P < 10^{-3}$) was found in the chi-square test, having a spare schedule tends to be a protective factor against anxiety ($P = 0.012$, OR = 0.367, 95%CI: 0.165-0.799) but not depression[19]. The part taken by social life and social relationships turns out to be a key strand in the fight against depression and lessen stressful life pressures[22,40,48,49]. Dyrbye *et al*[28], who drove a longitudinal study among 3743 United States medical students from 2010 to 2014, noticed that students who avowed having low social support were more likely to manifest depressive features ($P < 10^{-3}$). Similarly, Turkish and Palestinian studies substantiated the strong correlation ($P < 10^{-3}$) that relates social interaction and social stand with the contingency of depression[24,35].

Satisfaction and dropping out ideas: Statistical analysis showed a strong correlation between students' dissatisfaction and depression ($P < 10^{-3}$). Unsatisfaction is, then, considered a risk factor for developing depression. These data closely resemble findings from other studies. Pokhrel *et al*[19] demonstrated that satisfied students in Nepal were less prone to depression (OR = 0.51, 95%CI: 0.33-0.80). Similarly, discontented KSA medical students tend to be more depressed than their peers ($P = 0.03$)[35]. Studies conducted in New Zealand[50] and Palestine[26] reported results in line with our study. The influence that satisfaction toward career choice has on students' mental health did not come out of anywhere. It arises from the reluctance to study medicine: Whether to please parents' desire to become a doctor or to go along with friends aiming to get higher social status. All of it ends by being hushed, knowing the reality of medicine[51].

Recommendations

As disclosed above, medical students are without a doubt prone to several mental afflictions. Therefore, preventing such distress among students should be a priority and a must.

Primary prevention is possible by supplying learners with seminars on time management, relaxation exercises, and mindfulness activities through counseling services such as the listening unit that has been established in our faculty. Finally, prioritizing students' welfare starts by providing space and needed materials to enhance students' physical exercises and group activities, delivering variable and healthy meals in university restaurants, and revising students' schedules to suit their academic, physical, and psychological needs.

Limitations

Overall, the authors acknowledge some limitations to this study. Being a descriptive cross-sectional study, causal links between the correlations could not be inaugurated. Preferably, further studies should be surveyed in longitudinal, prospective, and multicenter designs aiming to yield a greater overview of the circumstances. Even though the number of students who participated in this survey is much higher than those carried out in Tunisian and neighboring studies, a larger sample size would have risen the diligence and exactness of our study.

As our study was based on self-administrated questionnaires and all data employed were self-reported, it is possible that students could have understated or overstated their depressive symptoms. The choice, itself, of participating in the online survey may mirror some level of bias related to the personal traits and characteristics of the students. We have estimated the occurrence of depression among medical students using a self-reported inventory (BDI-II), there were no clinical assessments supervised by psychiatrists. Consequently, the diagnostic value may be restricted, and further psychiatric interviews are required to validate our results. Other students' characteristics that were correlated to the development of depressive symptoms were not explored among participants, such as emotional intelligence, coping skills, social support, religious beliefs, personality characteristics, and substance use disorders.

CONCLUSION

These findings give insight into Tunisian medical students' mental health issues and comorbidities. It is a hopeful request for decision-makers and academic authorities to take serious measures and offer effective interventions to minimize the currency of psychological distress among this subpopulation. To date, this is the largest study on depression among Tunisian and Maghrebian medical students. Yet, further research is recommended to explore other correlated factors and to evaluate the effectiveness of these measures on depression levels among medical students.

ARTICLE HIGHLIGHTS

Research background

Most medical schools in the world (including Tunisia) still recruit their students based solely on the university entrance exam score. Students' motivation, though being a crucial conjecture in their academic performance and well-being, has never been conventionally and structurally assessed in Tunisia. As a result, many students simply choose the medical field due to social codes, family influences, and cultural norms.

Research motivation

It is crucial for an educational institution to assess the mental status of students and its associated factors.

Research objectives

To assess the prevalence of depressive symptoms among Tunisian medical students and to evaluate its associated factors.

Research methods

This is an online survey of students from the four Tunisian medical faculties using Beck's depression questionnaire.

Research results

Sixty-four percent ($n = 728$) of the participants had depressive symptoms. Female gender, low socioeconomic level,

smoking habits and history of mental disorder, performing leisure and physical activities, satisfaction toward a career choice, and happiness perception were the main prognostic factors for depression among medical students.

Research conclusions

These findings give insight into mental health issues and comorbidity among Tunisian medical students. It is a hopeful request for decision-makers and academic authorities to take serious measures and offer effective interventions to minimize the currency of psychological distress among this subpopulation.

Research perspectives

Further studies are needed to explore other correlated factors (such as emotional intelligence, coping skills, social support, religious beliefs, and personality characteristics) and to evaluate the effectiveness of these measures on depression levels among Tunisian medical students.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Correlation and pathways of behavioral activation systems mediating physical activity level and depressive symptoms among college students

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Abstract

BACKGROUND

Depression is a common mental disorder among college students. The main symptoms include being persistent low mood, sad emotional experiences, lack of pleasure, listlessness, and impaired cognitive function accompanied by tendencies of self-harm and suicide.

AIM

To clarify the pathways and effects of the behavioral activation system between physical activity and depressive symptoms in college students with depressive symptoms.

METHODS

This cross-sectional research screened 3047 college students. Of these, 472 had depressive symptoms, with a depression detection rate of 15.49%. Furthermore, 442 college students with depressive symptoms were analyzed. A one-way analysis of variance and Pearson's correlation, linear regression, and structural equation modeling analyses were used to explore the correlations and pathways of the interactions between the variables.

RESULTS

Depressive symptoms were significantly negatively correlated with physical activity (r = -0.175, $P < 0.001$), the behavioral activation system (r = -0.197, $P < 0.001$), and drive (r = -0.113, $P = 0.017$). Furthermore, it was negatively correlated with fun-seeking (FS) (r = -0.055, $P = 0.251$); however, it was not significant. Physical activity was significantly positively correlated with reward respons-

iveness (RR) (r = 0.141, *P* = 0.003) and drive (r = 0.124, *P* = 0.009) and not significantly positively correlated with FS (r = 0.090, *P* = 0.058). The mediating effect of RR between physical activity and depressive symptoms was significant [B = -0.025, 95% confidence interval (95%CI): -0.051 to -0.008, *P* = 0.001]. The direct and total effects of physical activity on depressive symptoms and were significant (B = -0.150, 95%CI: -0.233 to -0.073, *P* < 0.001; B = -0.175, 95%CI: -0.260 to -0.099, *P* < 0.001), respectively.

CONCLUSION

As physical activity levels increased, depression scores among college students decreased. The mediating effect of RR between physical activity and depressive symptoms was significant. Therefore, colleges and universities should encourage college students with depression to increase their physical activity and improve their behavioral activation system. Particular attention should be paid to RR, which may reduce the prevalence of depressive symptoms.

Key Words: College students; Physical activity; Depressive symptoms; Behavioral activation system; Mediating role

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Core Tip: This study explored the specificity of the behavioral activation system for physical activity and reward motivation in college students with different depressive symptom scores. Furthermore, the inter-relationships among the three variables were examined *via* a cross-sectional research design. Pathways of the behavioral activation system that mediated the effect of physical activity level on depressive symptoms in college students with depressive symptoms were clarified.

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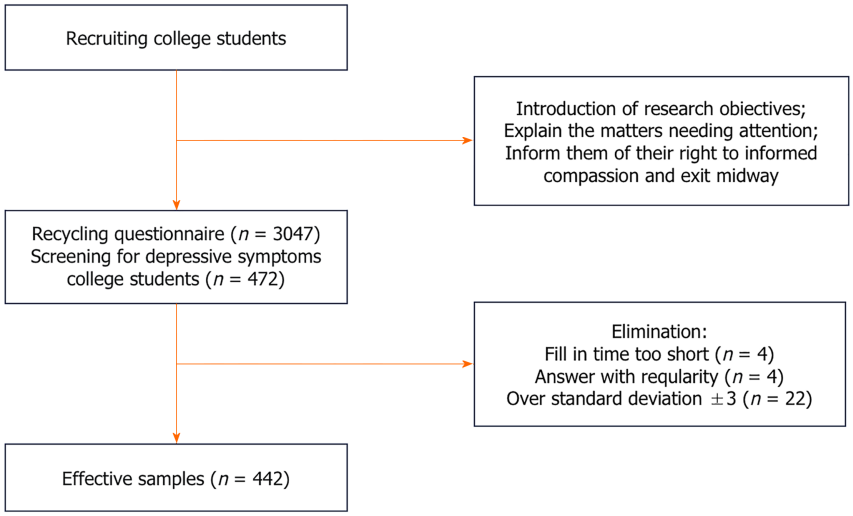
INTRODUCTION

Depression, a disabling mental disorder, seriously endangers the lives and health of people and ranks the 13th highest in the number of disability-adjusted life-years among all illnesses and injuries worldwide[1]. It is a common mental disorder among college students, with a detection rate of over 30%[2,3]. The main symptoms include persistent low mood, sad emotional experiences, lack of pleasure, listlessness, and impaired cognitive function, with tendencies of self-harm and suicide. The World Health Organization predicted that depression would rank first in the disease burden worldwide by 2030[4].

The behavioral activation system, also known as reward motivation, is located in the midbrain dopamine loop and refers to the convergent motivation for reward, promoting goal-directed behavior to obtain the reward, and producing positive emotions or hedonic pleasure experiences[5]. It is divided into three factors: Reward responsiveness (RR), drive, and fun-seeking (FS)[6]. Impaired reward function, or anhedonia, is a core symptom of depression, and deficits in the behavioral activation system can serve as functional deficits in depressive symptoms[7,8].

An inter-relationship between physical activity, depressive symptoms, and behavioral activation system exists. Appropriate physical activity significantly alleviates clinical symptoms in people with depressive symptoms[9-11] and reduces anxiety and depression levels in college students[12]. In addition, exercise is also strongly associated with behavioral activation system, such as enhancing the midbrain-striatal dopamine (DA) system and improving the brain reward function in adolescents[13]. Physical activity also positively affects the behavioral activation system, and thereby alleviates depressive symptoms.

Previous studies[7-11,13] examined the two-sided relationship between physical activity, behavioral activation system, and depressive symptoms. Physical activity enhanced the behavioral activation system and reduced depressive symptoms. Furthermore, the behavioral activation system acted as an influencing factor for depressive symptoms. However, whether the behavioral activation system intervened in the relationship between physical activity and depressive symptoms remains unclear. Furthermore, its pathways of actions, how it intervened through the three subdimensions of the behavioral activation system, and whether the effects were consistent also remain unclear. Therefore, this study conducted a cross-sectional research that aimed to provide a theoretical basis for a deeper understanding of the relationship between human behavior, emotion, and the nervous system. Furthermore, we aimed to provide a reference for researchers and college administrators. This study proposed the following research hypotheses: (1) Physical activity and the behavioral activation system would have specificity among college students with different depressive symptom scores; (2) Physical activity, the behavioral activation system, and depressive symptoms would be closely related; and (3) Behavioral activation system would mediate the relationship between physical activity and depressive symptoms with different effects of the sub-dimensions.



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Figure 1 Flow chart of the participants recruitment.

MATERIALS AND METHODS

Participants

This study used a cross-sectional research design. In total, 3047 college students were recruited online based on voluntary participation to complete a questionnaire. College students with depressive symptoms were screened *via* the Beck Depression Inventory (BDI)-II, and 472 students had depressive symptoms, with a depression detection rate of 15.49% (Figure 1). Inclusion criteria were participants who were college students, aged 18-26 years, had a score of ≥ 14 on the BDI-II, with a scores of 14-19, 20-28, and 29-63 indicating mild, moderate, and severe depression, respectively, and had no other psychiatric disorders and no brain injury. The exclusion criteria were participants who took drugs, such as barbiturates, benzodiazepines, and chloral hydrate, majored in sports, and had contraindications for exercise. After 30 invalid questionnaires with regular responses, a short response time (< 3 min), or outliers that exceeded the standard deviation ± 3 were excluded, 442 valid questionnaires (93.64%) were obtained. This study was approved by the Ethics Committee of the Shanghai University of Sport (102772021RT007).

Measures

General information questionnaire: Participants' basic information, such as age, sex, height, weight, and family status were obtained.

International physical activity questionnaire short form: This 7-item questionnaire has been widely used to measure physical activity among Chinese university students. Of these, six questions enquired regarding individuals' physical activity, which included high-intensity and moderate-intensity physical activity, and walking, and the frequency of different intensity activities for one week and the cumulative time per day. The weekly physical activity levels were calculated and divided into high, medium, and low groups according to the relevant criteria. The higher the group level, the greater the intensity of daily physical activity. This scale's retest reliability coefficient was 0.718[14].

Behavioral inhibition/activation system scale: A revised Chinese version by Li *et al*[15] was adopted with 18 items, which included two dimensions: Behavioral inhibition and activation. The behavioral activation dimension, also known as the behavioral activation system, was selected and contained three subfactors: RR, drive, and FS. Each item was scored on a scale from 1 (fully agree) to 4 (fully disagree). Cronbach's alpha was 0.759[15].

BDI-II: This widely used 21-item self-assessment scale assessed depressive symptoms. Responses were rated on a 4-point Likert scale that ranged from 0 (no symptoms) to 3 (severe symptoms). Total scores of 0-13, 14-19, 20-28, and 29-63 indicated no, mild, moderate, and severe depression, respectively. The internal consistency coefficient was 0.948[16].

Statistical analysis

Measures were expressed as mean ± SD, and the results were retained to three decimal places. For questionnaire data that were not missing at random, interpolation of the means of the same category was performed to avoid biased estimated coefficients *via* the simple deletion method. One-way analysis of variance and least significant difference post-hoc multiple tests were applied to compare the specificity of physical activity and behavioral activation system among college students with different depressive symptom scores. Pearson's correlation and linear regression analyses were performed to explore the relationships among physical activity, depressive symptoms, and behavioral activation system. Two-tailed tests were adopted for statistical inference of all parameters, and the test level α was set at 0.05. $P < 0.05$, $P < 0.01$, and $P < 0.001$ all indicated statistical significance.

Table 1 Differences in physical activity and behavioral activation system in college students with different depressive symptom scores

Variables	Whole (442)	Levels of depressive symptoms			F-value	*P* value	Post hoc multiple comparisons		
		Severe (*n* = 58)	Moderate (*n* = 190)	Mild (*n* = 194)			Severe *vs* Moderate	Severe *vs* Mild	Moderate *vs* Mild
Physical activity (MET-min/week)	1308 ± 954	944 ± 617	1333 ± 1003	1392 ± 967	5.149	0.006	0.006	0.002	0.535
Reward responsiveness	11.88 ± 2.033	11.03 ± 2.232	11.81 ± 2.043	12.21 ± 1.885	7.865	< 0.001	< 0.001	0.010	0.053
Drive	11.22 ± 2.064	10.71 ± 2.656	11.15 ± 2.008	11.45 ± 1.888	3.129	0.045	0.154	0.016	0.152
Fun-seeking	14.17 ± 2.270	13.78 ± 2.968	14.10 ± 2.217	14.36 ± 2.067	1.654	0.192	0.341	0.085	0.260

Table 2 Regression analysis of each variable

Independent variables	B	95%CI		Beta	Coefficient significance test		SE	Collinearity diagnostics	
		Lower limit	Upper limit		*t*-value	*P* value		Tolerance	VIF
Reward responsiveness	-0.176	-0.268	-0.084	-0.176	-3.766	< 0.001[a]	0.047	0.980	1.020
Physical activity	-0.116	-0.242	-0.058	-0.116	-3.217	0.001	0.047	0.980	1.020

[a]*P* < 0.001.

Model summary: F = 14.259[a]; R = 0.247; R^2 = 0.061; Adjusted R^2 = 0.057. VIF: Variance inflation factor; 95%CI: 95% confidence interval.

Harman's single factor test was used to examine the effects of common method bias. Structural equation modeling was conducted to examine the role of behavioral activation system in mediating the relationship between physical activity and depressive symptoms. The non-parametric percentage bootstrap method was adopted for parameter estimation in the path analysis. Number of samples was set at 5000, with a bias-corrected 95% confidence interval (95%CI) for the product of the mediated paths, without 0 defining the mediating effect as statistically significant. Data calculations were performed using SPSS Statistics version 23.0, and Amos version 23.0.

RESULTS

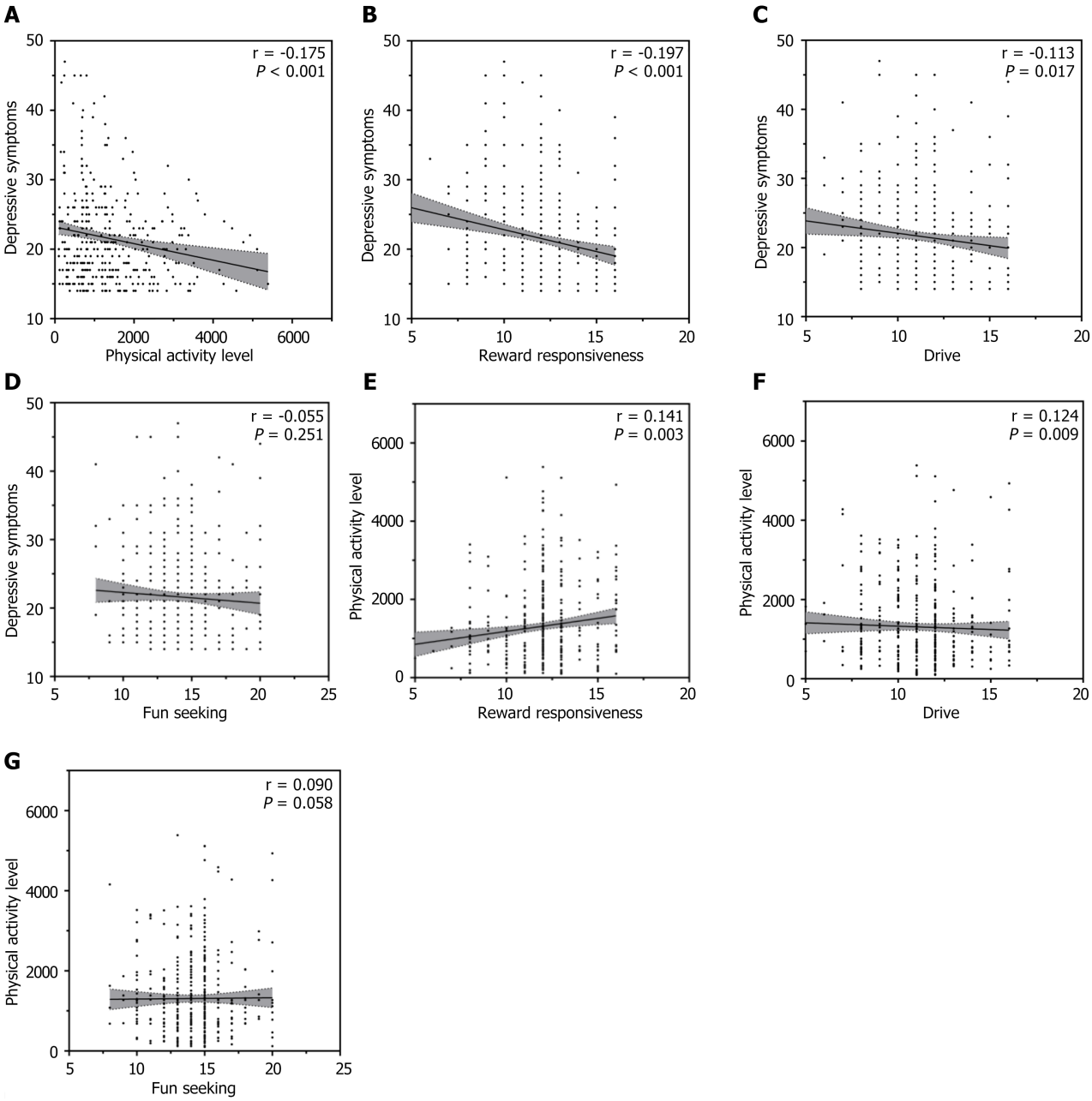
Specificity of physical activity and behavioral activation system in college students with different depressive symptom scores

There were no significant differences in FS behavior, physical activity, RR, and drive ($P < 0.05$) among college students with different depressive symptom scores. Post-hoc multiple comparisons indicated significant differences in physical activity and RR ($P < 0.05$) between college students with severe depressive symptoms and those with moderate depressive symptoms. In addition, there were also differences in physical activity, RR, and drive ($P < 0.01$) between those with severe depressive symptoms and those with mild depressive symptoms. Other indicators had no statistically significant differences. See Table 1 for further details.

Relationship between physical activity, depressive symptoms and behavioral activation system

Depressive symptoms were significantly negatively correlated with physical activity (r = -0.175, $P < 0.001$), RR (r = -0.197, $P < 0.001$), and drive (r = -0.113, $P = 0.017$). Furthermore, it was also negatively correlated with FS (r = -0.055, $P = 0.251$); however, it was not significant. Physical activity was significantly positively correlated with RR (r = 0.141, $P = 0.003$) and drive (r = 0.124, $P = 0.009$), and not significantly positively correlated with FS (r = 0.090, $P = 0.058$). Further details are shown in Figure 2.

To examine the extent of which physical activity and behavioral activation system explained depressive symptoms and explore the feasibility of the structural relationship model, depressive symptoms were considered as dependent variables, and physical activity, RR, drive, and FS as independent variables. Furthermore, a linear regression analysis was performed *via* stepwise regression. The goodness-of-fit of the prediction model was demonstrated (R = 0.247, R^2 = 0.061, adjusted R^2 = 0.057, and changed variable F = 10.349), which excluded drive and FS. As shown in Table 2, RR and physical activity were negative influencing factors, with 6.1% explanatory power for depressive symptom scores. The tolerance of each independent variable was > 0.1, and the variance inflation factor was < 5; thus, the effect of multicollinearity was excluded.



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Figure 2 Correlations among the variables. A: Depressive symptoms were significantly negatively correlated with physical activity; B: Depressive symptoms were significantly negatively correlated with reward responsiveness; C: Depressive symptoms were significantly negatively correlated with drive; D: Depressive symptoms were negatively, but not significantly, associated with fun-seeking; E: Physical activity was significantly positively correlated with reward responsiveness; F: Physical activity was significantly positively correlated with drive; G: Physical activity were positively, but not significantly, associated with fun-seeking.

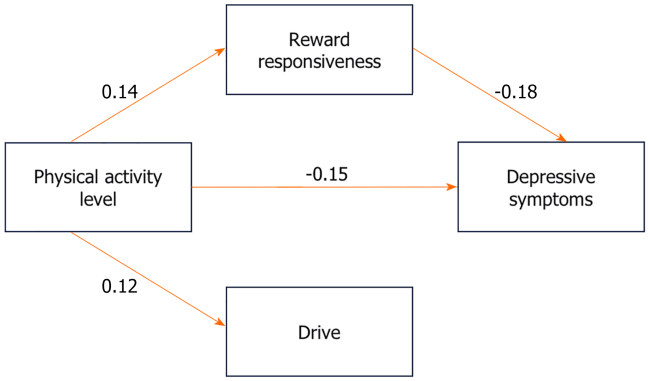
Construction and validation of a structural relationship model of indicators of physical activity, behavioral activation system, and depressive symptoms

To assess for common method bias, a validation factor analysis was conducted on the International Physical Activity Questionnaire, the Behavioral Activation System Scale, and the BDI *via* Harman's single factor test, nine factors with characteristic roots greater than 1 were obtained. The amount of variance explained by the first factor was 17.980%, which was less than the critical value of 40%. Therefore, the effect of common method bias was excluded. Based on the inter-relationships among physical activity, behavioral activation system, and depressive symptoms in college students, a model was established with physical activity, depressive symptoms, and behavioral activation system as the independent, dependent, and mediating variables, respectively. Mediated paths with insignificant coefficients were individually removed and recalculated until all mediated path coefficients passed the bootstrap significance test. Discrepancies divided by degrees of freedom (CMIN/df) = 0.286, root mean square residual (RMR) = 0.006, root mean square error of approximation (RMSEA) < 0.001, goodness-of-fit index (GFI) = 1.000, normed fit index (NFI) = 0.999, and comparative fit index (CFI) = 1.000 reached the reference standards of CMIN/df < 3, RMR < 0.05, RMSEA < 0.08, GFI, NFI, and CFI > 0.9[17], which indicated that the structural equation model fit well and was reasonable and reliable. The

Table 3 List of the intermediary effect coefficients

Types of effects	B	SE	Bias-corrected 95%CI		
			Lower limit	Upper limit	*P* value
Mediating effect of reward responsiveness	-0.025	0.011	-0.051	-0.008	0.001
Path coefficient of physical activity on drive	0.124	0.045	0.034	0.211	0.007
Direct effect	-0.150	0.041	-0.233	-0.073	< 0.001
Total effect	-0.175	0.040	-0.260	-0.099	< 0.001

95%CI: 95% confidence interval.



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Figure 3 Schematic diagram of the structural relationship model between physical activity, behavioral activation system, and depressive symptom indicators in college students with depressive symptoms. There are direct pathways and reward responsiveness-mediated indirect pathways between physical activity and depressive symptoms.

path analysis is shown in Figure 3, and the results of the mediating effect test are presented in Table 3. The path coefficients of physical activity on FS were not significant. Furthermore, those of FS and driving on depressive symptom scores were not significant, and were excluded. There were significant path coefficient for physical activity on drive (B = 0.124, 95%CI: 0.034 to 0.211, P = 0.007), mediating effect mediated by RR (B = -0.025, 95%CI: -0.051 to -0.008, P = 0.001), direct effect of physical activity on depressive symptoms (B = -0.150, 95%CI: -0.233 to -0.073, P < 0.001), and total effect of physical activity on depressive symptoms (B = -0.175. 95%CI: -0.260 to -0.099, P < 0.001).

DISCUSSION

These results showed that the higher the level of physical activity among college students with depressive symptoms, the higher the behavioral activation system and lower their depressive symptom scores. Furthermore, the direct effect of physical activity on depressive symptoms was significant. The results supported those of previous studies on the relationship between behavioral activation system and depressive symptoms. Furthermore, our findings were generally consistent with previous results. Takagaki *et al*[18] found a negative association between the behavioral activation system and depressive symptoms among 18-19 years old college students with depressive symptoms in a Japanese University. Absence of pleasure was a core symptom of depression[19] which was related to the dysfunction of the brain's DA reward system[20]. Deficits in the reward system served as a susceptibility factor and predictor of depression, with state independence and heritability[21,22]. A cross-sectional study found that college students with higher levels of physical activity had lower detection rates of depressive symptoms and insufficient physical activity was a risk factor for depressive symptoms among college students. Experimental studies confirmed that increased physical activity was effective in improving depressive symptoms and stimulated the secretion of neurotransmitters, which increased the behavioral activation system and also alleviated depressive symptoms.

This study showed that only RR mediated the relationship between physical activity and depressive symptoms. Physical activity promoted the secretion of neurotransmitters, such as DA in the brain, enhanced the neuroplasticity of the DA system, and improved the reward function. This enhanced the RR and contributed to the maintenance and regulation of good emotions in individuals, promoted the generation of positive emotions, and suppressed negative emotions[23]. High reward responses acted as a protective factor against depression[24]. Furthermore RR purely reflected extroversion and convergent motivation[25], which maintained and regulated individual behavior. Hence, impulsive behaviors that met short-term interests were subordinated to needs more closely related to the individual's long-term

interests[26]. High RR prompted a positive response to rewards. It enhanced an individual's ability to obtain pleasurable experiences to avoid the exacerbation of their depressive symptoms[27,28]. Only the RR pathway mediated the relationship between physical activity and depressive symptoms. A possible reason was that RR, as the initial evaluation of reward, measured early "reward interest," "goal-drive", and "persistence." Furthermore, its effect on depressive symptoms may precede the other two dimensions. Reasons why drive and FS did not mediate the relationship between physical activity and depressive symptoms were drive referred to the degree of willingness to exert effort to obtain a reward and measured late "reward responsiveness" and "impulsivity;" FS was a continuous evaluation of the reward. Hence, drive and FS were more significant for major depression, and better predictors of treatment effect[29,30]. Our participants had different conditions, and relatively few individuals reported severe depression symptoms.

This study has some limitations. First, the data were from subjective reports, which may have some bias. Furthermore objective indicators are recommended for future measurements. This study was conducted as a cross-sectional study. Hence, longitudinal studies are required to further confirm the pathways of action.

CONCLUSION

The higher the level of physical activity, the higher the behavioral activation system and lower the depressive symptom score in college students with depression. Furthermore, there was only one pathway of action in the behavioral activation system, RR, which had a significant mediating effect between physical activity and depressive symptoms. Therefore, colleges and universities should encourage college students with depression to increase their physical activity and improve their behavioral activation system. Particular attention should be paid to RR, which may reduce the prevalence of depressive symptoms.

ARTICLE HIGHLIGHTS

Research background

Depression is a common mental disorder among college students. Key symptoms include persistent depressed mood, sad emotional experiences, lack of pleasure, listlessness, and impaired cognitive function, accompanied by self-harm and suicidal tendencies.

Research motivation

Reduce the prevalence of depressive symptoms in college students.

Research objectives

Elucidating pathways and effects of behavioral activation systems between physical activity and depressive symptoms in college students with depressive symptoms.

Research methods

One-way analysis of variance and Pearson correlation, linear regression, and structural equation modeling were used to explore the correlation and pathway of interactions between variables.

Research results

The mediating effect of reward responses between physical activity and depressive symptoms was significant [B = -0.025, 95% confidence interval (95%CI): -0.051 to -0.008, $P = 0.001$]. The direct and total effects of physical activity on depressive symptoms were significant ((B = -0.150, 95%CI: -0.233 to -0.073, $P < 0.001$; B = -0.175, 95%CI: -0.260 to -0.099, $P < 0.001$, respectively).

Research conclusions

Colleges and universities should encourage college students with depression to increase physical activity and improve behavioral activation systems. Particular attention should be paid to the ability to reward responses, which may reduce the prevalence of depressive symptoms.

Research perspectives

It is recommended to use objective measurement tools in future measurements; longitudinal studies are needed to further define the course of action.

FOOTNOTES

Author contributions: Zhu JH wrote the original manuscript and collected the data; Li SF collected and analyzed the data; Wang P wrote part of the manuscript; Xin X collected the data; Zhao Q curated the data; Chen SC curated the data; Wang X reviewed and edited.

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Institutional review board statement: This study was approved by the ethical committee of Shanghai University of Sport (102772021RT007), and all procedures were performed according to the relevant guidelines and regulations.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Observational Study

Analysis of mental health status and related factors in patients with acute cerebral infarction

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Abstract

BACKGROUND

Acute cerebral infarction (ACI) is characterized by a high incidence of morbidity, disability, recurrence, death and heavy economic burden, and has become a disease of concern in global researchers. As ACI has serious effects on patients' physical status, life and economy, often causing anxiety, depression and other psychological problems, these problems can lead to the aggravation of physical symptoms; thus, it is very important to understand the factors affecting the mental health of these patients.

AIM

To understand the elements that affect the mental health of patients who have suffered an ACI.

METHODS

A questionnaire survey was conducted among patients with ACI admitted to three tertiary hospitals (Quanzhou First Hospital, Fuqing City Hospital Affiliated to Fujian Medical University, and the 900 Hospital of the Joint Service Support Force of the People's Liberation Army of China) in Fujian Province from January 2022 to December 2022 using the convenience sampling method. ACI inpatients

who met the inclusion criteria were selected. Informed consent was obtained from the patients before the investigation, and a face-to-face questionnaire survey was conducted using a unified scale. The questionnaire included a general situation questionnaire, Zung's self-rating depression scale and Zung's self-rating anxiety scale. All questionnaires were checked by two researchers and then the data were input and sorted using Excel software. The general situation of patients with ACI was analyzed by descriptive statistics, the influence of variables on mental health by the independent sample *t* test and variance analysis, and the influencing factors on psychological distress were analyzed by multiple stepwise regression.

RESULTS

The average age of the 220 patients with ACI was 68.64 ± 10.74 years, including 142 males and 78 females. Most of the patients were between 60 and 74 years old, the majority had high school or technical secondary school education, most lived with their spouse, and most lived in cities. The majority of patients had a personal income of 3001 to 5000 RMB yuan per month. The new rural cooperative medical insurance system had the largest number of participants. Most stroke patients were cared for by their spouses and of these patients, 52.3% had previously smoked. Univariate analysis showed that gender, age, residence, course of disease, number of previous chronic diseases and smoking history were the main factors affecting the anxiety scores of patients with ACI. Age, living conditions, monthly income, course of disease and knowledge of disease were the primary variables influencing the depression score in patients with ACI. The findings of multivariate analysis revealed that the course of disease and gender were the most important factors influencing patients' anxiety scores, and the course of disease was also the most important factor influencing patients' depression scores.

CONCLUSION

Long disease course and female patients with ACI were more likely to have psychological problems such as a high incidence of emotional disorders. These groups require more attention and counseling.

Key Words: Acute cerebral infarction; Mental health; Self-rating depression scale; Self-rating anxiety scale; Influencing factor; Correlation analysis

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Core Tip: In recent years, research on acute cerebral infarction has not only focused on the effects of the infarction on the body, but also the psychological effects. In this study, we found that long disease course may be the main factor leading to psychological problems in patients, and female patients with a high incidence of emotional disorders are more likely to have psychological problems. Such groups require more attention and psychological counseling.

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INTRODUCTION

Acute cerebral infarction (ACI) has become a disease of concern in global researchers due to its high incidence of morbidity, disability, recurrence, death and heavy economic burden[1,2]. Most patients have different degrees of limb function, cognitive function and other disorders following sudden ACI. Patients find it difficult to accept physical changes which have a greater impact on their psychological status. These cannot be resolved in a short period of time, and there are some emotional changes such as suspicion and anxiety. Long-term negative emotions are psychological burdens, which affect physical and mental health[3-5]. Early detection of psychological problems, exploring the source of these psychological problems, providing targeted solutions, reducing patients' psychological disorders while improving the recovery in limb function or cognition, and promoting rehabilitation are essential. Therefore, it is necessary to carry out a cross-sectional survey to understand the influencing factors on mental health status in patients with ACI, examine the key factors affecting mental health, improve the mental health status of patients with ACI, and pave the way for early clinical intervention.

MATERIALS AND METHODS

Study population and data collection

From January 2022 to December 2022, a questionnaire survey was conducted in patients with ACI admitted to three tertiary hospitals in Fujian Province (Quanzhou First Hospital, Fuqing City Hospital Affiliated to Fujian Medical University, and the 900 Hospital of the Joint Service Support Force of the People's Liberation Army of China).

Inclusion criteria were: (1) Diagnosis consistent with that in the Chinese acute stroke clinical research consensus; (2) High research compliance; (3) Basic listening and speaking ability; and (4) Patients with a temporary stable condition and clear consciousness.

Exclusion criteria were: (1) Patients with language communication, cognitive, hearing or mental disorders; (2) Those with severe respiratory failure, malignant tumor, liver, renal, and cardiac dysfunction; and (3) Incomplete clinical data or participation in other research.

All patients with ACI who met the inclusion requirements were included in the study. Before the investigation, consent was obtained from the subjects and the informed consent was signed. A unified scale was used to conduct a face-to-face questionnaire survey. Those with good reading and writing ability completed the questionnaire. If the patients had difficulty in completing the questionnaire, the researcher used a unified guidance language to describe the questions. When the patient understood the questions, the survey was completed according to the patient's opinions. The researcher collected and checked the questionnaires, and corrected any errors.

General information questionnaire

This questionnaire included demographic characteristics (gender, age, education level, marital status, medical insurance type, inpatient caregivers, smoking history, *etc*.) and disease-related data (course of disease, type of stroke, number of strokes, past chronic disease status, *etc*).

Assessment of anxiety and depression

To evaluate potential anxiety and depression, the Chinese versions of Zung's self-rating depression scale (SDS) and Zung's self-rating anxiety scale (SAS) were utilized. The commonly used SAS and SDS measures are quick and practical tools for assessing respondents' signs of anxiety and depression, and they have strong reliability and validity in the Chinese population. Each scale has 20 items that are rated on a scale of 1 to 4 to evaluate the assertions (rarely, occasionally, frequently, or always). The standard scale was created by multiplying the 20-80 point range of the overall score by 1.25. The higher the score, the more severe the anxiety or depression. According to the findings of the Chinese norm, the cut-off value of the SDS standard score was 53 points; mild depression was defined as 53-62 points, moderate depression as 63-72 points, and severe depression as more than 73 points. The SAS standard deviation cutoff was 50 points, with mild anxiety being between 50 and 59 points, moderate anxiety being between 60 and 69 points, and severe anxiety being more than 69 points.

Statistical analysis

All questionnaires were checked by two researchers, and then Excel software was used for data entry and collation. The SPSS26.0 program was utilized for data analysis. Descriptive statistical analysis was used for the general situation of patients with ACI. The independent sample *t* test and variance analysis were used to analyze the influence of each variable on mental health. Multiple stepwise regression analysis was used to analyze the influencing factors of psychological distress. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics of patients with ACI

Demographic characteristics of the 220 patients with ACI (Table 1).

Disease-related information on patients with ACI

The disease course, frequency of onset, history of hypertension, history of diabetes, history of coronary heart disease, and history of chronic diseases patients with ACI was counted (Table 2).

Mental health status of patients with ACI

Among the 220 patients with ACI in this survey, 122 had depression, including 73 cases of mild depression, 39 cases of moderate depression, and 10 cases of severe depression. One hundred and sixty-three cases had anxiety, including 65 cases of mild anxiety, 61 cases of moderate anxiety, and 37 cases of severe anxiety (Table 3).

Effects of demographic sociological characteristics on mental health

The SAS score and SDS score of ACI patients were used as dependent variables, and gender, age, occupation, education level, marital status, living conditions, place of residence, personal monthly income, type of medical insurance, inpatient nursing staff, and smoking history were used as independent variables for univariate analysis. The results showed that gender, age, living conditions and smoking history were the main factors affecting the SAS score of ACI patients. Age, living conditions and personal monthly income were the main factors affecting the SDS score of ACI patients (Table 4).

Table 1 Demographic characteristics of acute cerebral infarction patients

Characteristics	Classification	*n*	Constituent ratio
Gender	Male	142	64.5%
	Female	78	35.5%
Age (yr)	≤ 59	49	22.3%
	60-74	94	42.7%
	≥ 74	77	35.0%
Degree of education	Primary school and below	39	17.7%
	Junior middle school	54	24.5%
	High school/technical secondary school	91	41.4%
	College degree or above	36	16.4%
Marital status	Married	134	60.9%
	Bereft of one's spouse	26	11.8%
	Divorce or other	60	27.3%
Living situation	Live with parents	10	4.5%
	Live with children	41	18.6%
	Live with partner	108	49.1%
	Living alone	61	27.7%
Domicile	City	114	51.8%
	Village	106	48.2%
Monthly profit (yuan)	≤ 1000	17	7.7%
	1001-3000	75	34.1%
	3001-5000	76	34.5%
	≥ 5001	52	23.6%
Medical insurance type	Medical insurance for urban employees	63	28.6%
	Medical insurance for urban residents	40	18.2%
	New rural cooperative	95	43.2%
	Self-paying	22	10.0%
Caregiver	Parents	11	5.0%
	Spouse	114	51.8%
	Children	76	34.5%
	Other	19	8.6%
History of smoking	No	105	47.7%
	Yes	115	52.3%

Effects of ACI on mental health

The SAS score and SDS score of stroke patients were used as dependent variables, and the duration of disease, number of strokes, history of hypertension, history of diabetes, history of coronary heart disease, number of previous chronic diseases, and knowledge were used as independent variables for univariate analysis. The results showed that the course of disease, chronic history and the number of previous chronic diseases were the main factors affecting the SAS score of ACI patients. The course of disease and the status of knowledge of the disease were the main factors affecting the SDS score of patients with ACI (Table 5).

Multivariate analysis of anxiety in patients with ACI

The data obtained from this survey were analyzed by stepwise regression analysis, the SAS score in patients with ACI was used as the dependent variable, and the variables that showed statistically significant SAS scores in the patient data (gender, age, location, disease course, number of chronic diseases, and smoking history) as independent variables. The

Table 2 Disease-related data of acute cerebral infarction patients

Factors	Classification	*n*	Constituent ratio
Course of disease	1-6 mo	96	43.64%
	7-12 mo	73	33.18%
	1-2 yr	36	16.36%
	More than 2 yr	15	6.82%
Number of ACIs	One	122	55.45%
	More than two	98	44.55%
History of hypertension	Yes	132	60.00%
	No	88	40.00%
History of diabetes	Yes	117	53.18%
	No	103	46.82%
History of coronary heart disease	Yes	109	49.55%
	No	111	50.45%
Number of previous chronic diseases	0	17	7.73%
	1	75	34.09%
	2	101	45.91%
	3	27	12.27%
Informed status of ACI	Fully informed	97	44.09%
	Partially informed	73	33.18%
	Completely uninformed	50	22.73%

ACI: Acute cerebral infarction.

Table 3 Mental health status of acute cerebral infarction patients

Factors	Classification	Number	Constituent ratio	mean ± SD
SDS	Without	93	42.27%	43.31 ± 7.49
	M	73	33.18%	57.29 ± 2.74
	M	39	17.73%	66.51 ± 2.68
	S	10	4.55%	76.30 ± 1.64
SAS	Without	57	25.91%	43.09 ± 8.86
	M	65	29.55%	52.85 ± 10.03
	M	61	27.73%	60.38 ± 8.28
	S	37	16.82%	75.92 ± 4.97

SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

findings demonstrated that gender and progression of the illness were factors in the regression model (Table 6).

Multivariate analysis of depression in patients with ACI

The data obtained from this survey were analyzed by stepwise regression analysis, the SDS score in patients with ACI was used as the dependent variable, and the variables that showed statistically significant SAS scores in the patient data (age, place of residence, disease course, personal monthly income, and disease awareness) as independent variables. The findings demonstrated that the disease course was a factor in the regression equation (Table 7).

Table 4 Influence of sociological characteristics of the population on mental health

Factors	Classification	SAS (mean ± SD)	*F/t* value	*P* value	SDS (mean ± SD)	*F/t* value	*P* value
Gender	Male	54.74 ± 11.05	8.577[1]	0.004	52.36 ± 11.31	0.293[1]	0.589
	Female	62.5 ± 13.63			57.59 ± 11.78		
Age (yr)	≤ 59	51.33 ± 12.67	10.504	< 0.001	49.35 ± 11.18	8.878	< 0.001
	60-74	57.49 ± 11.42			53.67 ± 11.39		
	≥ 74	61.42 ± 12.38			57.97 ± 11.34		
Degree of education	Primary school and below	58.05 ± 12.82	0.494	0.687	55.38 ± 13.83	1.096	0.352
	Junior middle school	58.3 ± 11.05			53.15 ± 10.13		
	High school/technical secondary school	57.67 ± 13.43			55.33 ± 11.25		
	College degree or above	55.22 ± 12.36			51.72 ± 12.60		
Marital status	Married	57.51 ± 12.32	1.687	0.188	53.88 ± 11.88	1.559	0.213
	Bereft of one's spouse	61.23 ± 12.30			57.96 ± 9.28		
	Divorce or other	55.83 ± 13.04			53.33 ± 12.18		
Living situation	Live with parents	48.00 ± 10.71	3.849	0.01	44.40 ± 11.32	3.923	0.009
	Live with children	61.83 ± 10.76			57.88 ± 11.32	2.4	
	Live with partner	57.36 ± 12.82			53.61 ± 11.99	3.4	
	Living alone	56.36 ± 12.61			54.43 ± 10.72		
Domicile	City	55.97 ± 12.30	3.494[1]	0.063	54.18 ± 11.05	0.002[1]	0.96
	Village	59.12 ± 12.69			54.25 ± 12.46		
Monthly profit (yuan)	≤ 1000	56.35 ± 12.52	1.9	0.131	50.00 ± 15.36	2.845	0.039
	1001-3000	56.57 ± 11.94			54.13 ± 12.24		
	3001-5000	60.17 ± 12.45			56.88 ± 10.45		
	≥ 5001	55.27 ± 13.26			51.81 ± 10.76		
Medical insurance type	Medical insurance for urban employees	57.25 ± 13.46	1.245	0.294	55.60 ± 10.69	1.063	0.366
	Medical insurance for urban residents	54.3 ± 11.02			51.43 ± 11.08		
	New rural cooperative	58.78 ± 12.79			54.40 ± 12.64		
	Self-paying	58.41 ± 11.14			54.50 ± 11.53		
Caregiver	Parents	48.55 ± 5.09	2.189	0.09	51.36 ± 12.75	1.012	0.388
	Spouse	58.00 ± 13.10			53.80 ± 11.29		
	Children	58.41 ± 11.36			55.84 ± 12.41		
	Other	55.95 ± 15.26			51.84 ± 10.81		
History of smoking	No	55.63 ± 12.16	5.422[1]	0.021	53.39 ± 11.91	1.186[1]	0.277
	Yes	59.53 ± 12.77			55.11 ± 11.51		

[1]*t* value.
ACI: Acute cerebral infarction; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

DISCUSSION

ACI is a sudden cerebrovascular disease. It is an acute attack when the patient's brain is blocked by blood vessels such as coronary arteries[6,7]. Due to the close connection between the cerebrovascular and central nervous system, patients with ACI often have a poor prognosis. Even after treatment, neurological dysfunction may persist. Some patients are prone to unpleasant feelings such as depression and anxiety during the onset of the disease, and then sleep disorders, neurasthenia and other symptoms, such psychological changes may be related to the occurrence of nerve defects[8-10]. In recent years, the study of ACI has not only focused on the effects on the body, but psychological effects have received more and more attention[11-13]. Patients with anxiety and depression often have a poor prognosis, longer recovery time and are

Table 5 Effects of acute cerebral infarction on mental health

Factors	Classification	SAS (mean ± SD)	*F/t/Welch* value	*P* value	SDS (mean ± SD)	*F/t/Welch* value	*P* value
Course of disease	1-6 mo	47.66 ± 9.80	72.127	< 0.001	46.36 ± 10.63	56.835[2]	< 0.001
	7-12 mo	62.97 ± 7.48			59.12 ± 7.83		
	1-2 yr	68.17 ± 9.99			58.81 ± 8.51		
	More than 2 yr	68.13 ± 6.55			69.53 ± 5.76		
Number of ACIs	One	56.63 ± 13.34	1.286[1]	0.258	53.10 ± 13.18	2.674[1]	0.103
	More than two	58.56 ± 11.48			55.60 ± 9.50		
History of hypertension	Yes	57.11 ± 12.28	0.309[1]	0.579	53.86 ± 11.60	0.293[1]	0.589
	No	58.07 ± 13.01			54.74 ± 11.96		
History of diabetes	Yes	57.14 ± 13.01	0.198[1]	0.657	54.09 ± 10.83	0.03[1]	0.863
	No	57.89 ± 12.07			54.36 ± 12.72		
History of coronary heart disease	Yes	57.02 ± 12.43	0.305[1]	0.581	54.36 ± 11.54	0.033[1]	0.857
	No	57.95 ± 12.72			54.07 ± 11.96		
Number of previous chronic diseases	0	64.94 ± 12.36	2.595	0.050	59.53 ± 10.33	2.277	0.081
	1	55.73 ± 12.07			52.09 ± 13.20		
	2	57.76 ± 12.34			55.13 ± 10.78		
	3	56.67 ± 13.67			53.33 ± 10.71		
Informed status of ACI	Fully informed	57.04 ± 12.63	2.444	0.089	55.14 ± 11.22	5.161	0.006
	Partially informed	55.84 ± 11.99			50.88 ± 12.02		
	Completely uninformed	60.78 ± 12.87			57.28 ± 11.31		

[1]*t* value.
[2]Welch value.
ACI: Acute cerebral infarction; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

Table 6 Multivariate analysis of anxiety in patients with acute cerebral infarction

Variable	B	SE	Beta	*t* value	*P* value	95%CI
Constant	29.551	2.164		13.654	< 0.001	25.286-33.817
Course of disease	8.918	0.638	0.658	13.981	< 0.001	7.661-10.176
Sex	8.356	1.232	0.319	6.781	< 0.001	5.928-10.785

CI: Confidence interval.

Table 7 Multivariate analysis of depression in patients with acute cerebral infarction

Variable	B	SE	Beta	*t* value	*P* value	95%CI
Constant	41.149	1.457		28.252	< 0.001	38.279-44.02
Course of disease	8.769	0.7	0.647	12.524	< 0.001	7.389-10.149

CI: Confidence interval.

more likely to relapse[13,14]. Therefore, this study analyzed the influencing factors on mental health in patients with ACI, with the hope of identifying the key factors affecting mental health.

The SAS score and SDS score in the 220 patients with ACI included in this study were statistically significant. The total SAS score was 57.49 ± 12.56, which was significantly higher than the standard cut-off value. The total SDS score was 54.21 ± 11.73, which was significantly higher than the standard cut-off value, indicating that psychological problems are common in patients with ACI in China. The results of univariate analysis showed that gender, age, residence, course of disease, number of chronic diseases and smoking history were the primary elements influencing the anxiety score in patients with ACI. Age, living conditions, monthly income, course of disease and knowledge of ACI were primary elements influencing the depression score in patients with ACI. The analysis results showed that female patients had more severe anxiety than male patients. The levels of anxiety and depression increased with age. Similar to previous research results, a possible reason for this is that women and the elderly belong to a high-risk group with emotional disorders[15-17], and psychological problems are more likely to occur after ACI. The SAS and SDS scores of patients living with their children were higher, which matched the outcomes of earlier studies[18,19]. This may be because patients living with their children often need to take care of their families, and the lack of ability regarding family care after infarction leads to serious anxiety. The longer the disease course, the higher the SAS and SDS scores in patients, which matched the outcomes of earlier studies[20,21], and might be the result of an aggravation of psychological problems caused by long-term distress; the anxiety score in patients without a history of chronic disease was highest, which may be due to the increase in psychological pressure caused by the patient's abilities in their previous healthy state and their sudden need for care. The depression score in patients with ACI and higher monthly income was greatest, which may be due to the impact on work and income after illness, resulting in psychological problems. Patients who do not understand the disease have higher depression scores, which may be due to the fact that patients do not understand their disease status and do not know why they are more likely to worry about hospitalization, resulting in psychological problems. Furthermore, multivariate analysis showed that the course of disease and gender were the key factors affecting the anxiety score in patients, and the course of disease was also the key factor affecting the depression score in patients. According to these findings, psychological issues are more likely to occur in patients who have had their disorder for a longer period of time and in women.

The limitation of this study is that the sample size is too small to fully analyze more factors affecting the mental health status of ACI patients. In future studies, we will continue to collect data of ACI patients, and further evaluate the key factors affecting the mental health of ACI patients in a more comprehensive way, as well as the mediating and regulating effects of other influencing factors.

CONCLUSION

In summary, patients with ACI generally have psychological issues including despair and anxiety. A long disease course may be the main factor leading to psychological problems in patients, and female patients are more likely to have psychological problems such as a high incidence of emotional disorders. Such groups require more attention and psychological counseling.

ARTICLE HIGHLIGHTS

Research background

Acute cerebral infarction (ACI) is a sudden cerebrovascular disease. ACI occurs when the patient's brain is blocked by coronary arteries and other blood vessels, resulting in ischemia and hypoxia. Even after receiving treatment, there may be persistent neurological dysfunction. Patients with anxiety and depression tend to have a poor prognosis, take longer to recover and are more likely to relapse.

Research motivation

This study analyzed the factors affecting the mental health of patients with ACI, with the hope of identifying the key factors affecting mental health.

Research objectives

The object of this study is to improve the mental health status of patients with ACI, and pave the way for early clinical intervention.

Research methods

A questionnaire survey was conducted among patients with ACI admitted to three tertiary hospitals in Fujian Province from January 2022 to December 2022 using the convenience sampling method. Patients with ACI who were inpatients and met the inclusion criteria were selected. A face-to-face questionnaire survey was conducted using a unified scale. To evaluate potential signs of anxiety and depression, the Zung's self-rating depression scale and Zung's self-rating anxiety scale were used. All questionnaires were checked by two researchers and then the data were input and sorted using Excel software. The general situation of ACI patients was analyzed by descriptive statistics, the influence of variables on mental

health by the independent sample *t* test and variance analysis, and the influencing factors on psychological distress were analyzed by multiple stepwise regression.

Research results

Univariate analysis showed that gender, age, residence, course of disease, number of previous chronic diseases and smoking history were the main factors affecting anxiety scores in ACI patients. Age, living conditions, monthly income, course of disease and knowledge of ACI were the main factors affecting the depression score in ACI patients. According to the results of the multivariate analysis, the course of disease and gender were the key factors affecting the anxiety score, and the course of disease was also the key factor affecting the depression score.

Research conclusions

Patients with ACI generally have psychological issues including depression and anxiety. A long disease course may be the main factor leading to psychological problems in patients, and female patients are more likely to have psychological problems such as a high incidence of emotional disorders. Such groups require more attention and psychological counseling.

Research perspectives

More patient records should be collected to more comprehensively evaluate the key factors affecting the mental health of patients with ACI.

FOOTNOTES

Author contributions: Chen QQ and Lin FM contributed equally to this work and are co-first authors. Chen QQ and Lin FM contributed to the study design and manuscript preparation; Chen DH, Ye YM, and Chen FF involved in the data acquisition; Gong GM and Huang SF participated in the statistical analysis; Peng SL reviewed the manuscript.

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ORIGINAL ARTICLE

Observational Study

International study of the Complex Stress Reaction Syndrome: Implications for transdiagnostic clinical practice

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Abstract

BACKGROUND

The debate regarding diagnostic classification systems in psychiatry (categorial *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions. We previously found a unique pattern of stress reaction in a study executed during the coronavirus disease 2019 pandemic using large representative samples in two countries, and termed it the Complex Stress Reaction Syndrome (CSRS).

AIM

To investigate CSRS, Type A (psychiatric symptoms, spanning anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)), with or without long-coronavirus disease (COVID) residuals (CSRS, Type B, neuropsychiatric symptoms spanning cognitive deficits and fatigue, excluding systemic symptoms). Our two-tailed hypothesis was that CSRS is a condition related to an unrecognized type of stress reaction in daily life in the general population (Type A) or that it is related to the severe acute respiratory syndrome coronavirus 2 infection and its long-COVID residuals (Type B).

METHODS

977 individuals in four continents (North America, Europe, Australia and the Middle East) completed the online study questionnaire in six languages using the Qualtrics platform. The study was managed by six teams in six countries that promoted the study on social media. The questionnaire assessed anxiety, depression, stress symptoms and PTSD (CSRS, Type A), cognitive deficits and fatigue (CSRS, Type B). The data were analyzed using Proportion Analyses, Multivariate Analysis of Co-Variance (MANCOVA), linear regression analyses and validated clinical cutoff points.

RESULTS

The results of the Proportion Analyses showed that the prevalence of 4 symptoms spanning anxiety, depression, stress symptoms, and PTSD was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups, and gender. This supports the transdiagnostic argument embedded in the CSRS (Type A). The same pattern of results was found in infected/recovered individuals. The prevalence of the 4 psychiatric symptoms combination was significantly greater than that of 5 and 6 symptoms, when adding cognitive deficits and fatigue, respectively. MANCOVA showed a significant three-way interaction (age × gender × continent). Further analyses showed that the sources of this three-way interaction were threefold relating to two sub-populations at-risk: (1) Individuals that self-identified as non-binary gender scored significantly higher on all 4 psychiatric symptoms of the CSRS, Type A at young age groups (< 50 years old) in North America compared to (self-identified) women and men located in the 4 continents studied, and to other ages across the adult life span; and (2) This pattern of results (CSRS, Type A) was found also in women at young ages (< 40 years old) in North America who scored higher compared to men and women in other continents and other ages. Linear regression analyses confirmed the MANCOVA results.

CONCLUSION

These results show a combined mental health risk factor related to stress reactivity, suggesting that the CSRS is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

Key Words: Transdiagnostic; Complex Stress Reaction Syndrome; Stress reactivity; Affective disorders; Debate in psychiatry

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Core Tip: The debate regarding diagnostic classification systems in psychiatry (categorial *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions and affective disorders. The results of this international study show a combined mental health risk factor related to stress reactivity and reduced positive affectivity, suggesting that the Complex Stress Reaction Syndrome (Type A) is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

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INTRODUCTION

The debate on diagnostic classification systems and the resulting crisis in psychiatry is evolving[1]. Many professionals doubt the validity of the categorical model, Diagnostic and Statistical Manual of mental disorders (DSM) and International Classification of Diseases (ICD), as clinical practice, supported by scientific evidence, shows that mixed symptomology is often presented by many patients without meeting the full criteria of any traditional diagnostic category[2]. Updated search in *Reference Citation Analysis* (https://www.referencecitationanalysis.com/), Google Scholar and PubMed, shows that the transdiagnostic approach is evolving and that cutting edge studies are published in very high-ranked journals[3-7].

There are at least four transdiagnostic new classification systems: Hierarchical Taxonomy to Psychopathology[8], Research Domain Criteria[9], Bipolar-Schizophrenia Network on intermediate phenotypes[10], and Neuroscience-Based Nomenclature[11]. These dimensional transdiagnostic approaches showed biological evidence of specific underlying mechanisms for several mental disorders[12-15]. However, others claim that the findings on underlying biological mechanisms relate to a too wide range of disorders, ruling out the option of differential diagnosis and more accurate derived prevention and treatment[15,16]. The option of including dimensional categories in the traditional classifications has yet to be discussed.

The debate in psychiatry has crucial implications for the diagnosis of stress reactions. Optimal stress reactions are prerequisites of adaptive coping from evolutionary perspectives[17-19]. However, stress reactions are patient-specific, environment-specific, and timing-specific. Therefore, they include a wide range of behaviors and emotional conditions, which cross traditional classification categories and are addressed only partially by these systems[12-14,20,21]. Of special interest is the condition of exposure to multiple stressors, investigated mostly in disaster situations such as flooding, pandemics, hurricanes, earthquakes, and wars[22-25]. In the etiological explanations of the traditional nosology, the interactions of individual differences in coping capacities with the number and extent of environmental stressors have not been evidence-based to date.

Specifically, we previously found a unique transdiagnostic pattern of stress reaction in a binational study using large representative samples in two countries, Italy and Israel, executed during the coronavirus disease 2019 (COVID-19) pandemic[26]. The results showed a transdiagnostic combination of four stress-related symptoms [anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)] that was significantly more prevalent than combinations of fewer symptoms. We termed this combination of four symptoms the Complex Stress Reaction Syndrome (CSRS). We found this pattern of results in the two countries despite cultural and language differences between the two countries and between the methodologies used, suggesting convergent validity of the CSRS.

The pattern of multiple associated symptoms has been widely reported by others regarding the COVID-19 pandemic's impacts on mental health[27-29]. According to WHO reports, 22% of the population develops mental health problems in a dimensional pattern, reactive to emergencies[30]. Accordingly, we related the CSRS to the COVID-19 situation and included CSRS, Type A (psychiatric symptoms) and Type B (psychiatric and neuropsychiatric symptoms in COVID-infected and recovered individuals, excluding systemic symptoms of long-COVID)[26,31]. However, the possibility that CSRS is relevant in the post-COVID era, to capture the mixed clinical picture resulting from concomitant daily stressors in the general population, has only recently been proposed[16].

In a recent paper, we outlined the detailed description of the conceptual development of the CSRS, including its origins in clinical practice and its uniqueness as one transdiagnostic category[16], rather than a total transdiagnostic denial of the traditional psychiatric classifications as suggested by others. The framework underpinning the current study presents an elaboration of the first validation of the CSRS in our published binational study[26], by the inclusion of participants located in four continents in this current study, beyond the validation of the CSRS in only two countries.

In the current multi-lingual international study, conducted across four continents, we aimed to investigate our two-tailed hypothesis that the CSRS is a condition related to the unrecognized type of stress reaction in daily life in the general population (Type A) or related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection and its long-COVID neuropsychiatric residuals (Type B).

MATERIALS AND METHODS

Institutional review board

Institutional review board approvals for this international study were provided by The Johns Hopkins University, Baltimore, Maryland, United States, and by Bar Ilan University, Ramat-Gan, Israel. The study survey used the Qualtrics platform (Qualtrics, Provo, Utah, United States) for data collection.

Sample

From a sample of 2024 individuals who approached the study questionnaire and partially completed it, 977 completed the entire study questionnaire, and this sample was used for the statistical analyses.

Inclusion criteria: Age > 18 years old.

Recruitment regions: Middle East, North America, Australia, Europe.

Activating recruitment teams: A team of research assistants executed the study on media platforms in each of the six active countries located in four continents. These teams were located in Israel, Jordan, Italy, Sweden, United States and Australia. Each team was led by at least one psychiatrist or psychologist.

Languages: The survey (*i.e.* the clinical research tools) was translated from English to 5 languages (Arabic, Hebrew, Italian, Swedish and German) using back translations to English for validation. All posts on the social media platforms were published in all 6 languages of the study to enhance recruitment.

Qualtrics: We uploaded the study survey in 6 languages on the Qualtrics platform. The data were saved on this platform and analyzed periodically for the recruitment rate. The final statistical analyses were executed using the data saved on this platform.

Study period: February 1, 2022-March 1, 2023.

Clinical research tools: We used the following clinical screening tools to identify mental health status (CSRS, Type A): Generalized anxiety disorder-7 (anxiety measure[32]; Cronbach's alpha = 0.931), patient health questionnaire-8[33] (depression measure; Cronbach's alpha = 0.903), perceived stress scale[34] (stress measure; Cronbach's alpha = 0.901), international trauma questionnaire[35] (a PTSD measure; Cronbach's alpha = 0.921). We also used neuropsychiatric measures for infected or recovered individuals (CSRS, Type B): (1) The Perceived Deficits Questionnaire-5, (a cognitive impairment measure[36]; Cronbach's alpha = 0.88); and (2) Fatigue[37], (Cronbach's alpha = 0.654). Participants were asked whether they were SARS-CoV-2 infected/recovered or not. These data were analyzed using validated clinical cutoff points to identify symptomatic conditions above the normative scores on each tool. Anonymity of participants was maintained throughout the study.

Participation time: Surveys took approximately 15 min to complete as measured in a pilot study before the onset of this research.

Recruitment

Instagram: We opened an account with promoting videos and photos related to the study and periodically added more related materials. The materials were translated and posted in all six languages of the study. The account displayed a link to the survey's international Qualtrics platform. Each post was user friendly.

Facebook: We used Facebook online groups to post a link to the survey. In the case of private Facebook groups, the research assistants in each active participating country contacted the group managers for permission.

Reddit: We promoted the study using this social media platform which is friendly and popular in the United States and Australia.

Online meetings: The international study teams in the six active countries conducted periodical, online meetings with the leading author and professional leads across each recruitment site to track the recruitment process and rate. To manage recruitment goals in each region, the leading author shared figures of the participants' rate per region, extracted from the data already gathered at those points.

Statistical analyses

The statistical approach included three steps: (1) We analyzed the frequency of all combinations of symptoms, to determine the most frequent combinations of two, three, four (CSRS, Type A), five and six (CSRS, Type B) symptoms. We then compared between the most prevalent combinations of each number of symptoms using Proportion Analyses; (2) Multivariate Analysis of Co-Variance (MANCOVA) to identify subpopulations at risk; and (3) We confirmed the identification of the subpopulations at risk by linear regression analyses.

RESULTS

This sample included 655 women, 296 men, and 26 individuals who self-identified as non-binary gender. Of those, 253 aged 18-29, 294 aged 30-39, 204 aged 40-49, 151 aged 50-59, and 75 aged above 60 years old.

All symptoms were significantly correlated (Table 1). Proportion Analyses showed that in the general population, the prevalence of the four-symptom combination (CSRS, Type A) Anxiety, Depression, Stress and PTSD (30.98%, 95%CI: 28-33.8) was greater than that of the most prevalent combination of three symptoms (Anxiety, Stress, and PTSD; 12.78%, 95%CI: 10.7-14.9, $P < 0.001$) and the most prevalent combination of two symptoms (Anxiety and Stress; 6.24%, 95%CI: 4.8-7.8, $P < 0.001$), as well as more prevalent than the one most prevalent symptom (Stress; 18.81%, 95%CI: 16.6-21.6, $P < 0.001$) (Table 2).

In the infected population we found the same pattern of results. As shown for the general population, in infected individuals the prevalence of the combination of four symptoms, Anxiety, Depression, Stress and PTSD (27%, 95%CI: 24.1-31.8) was greater than that of the most prevalent combination of three symptoms (Anxiety, Stress, and PTSD; 12.2%, 95%CI: 9.7-15.3, $P < 0.001$), greater than that of the most prevalent combination of two symptoms (Anxiety and Stress; 5.9%, 95%CI: 4.2-8.3, $P < 0.001$), and that of the one most prevalent symptom (Stress; 21%, 95%CI: 18-25, $P < 0.01$).

However, when we added long-COVID neuropsychiatric symptoms (Cognitive deficits and Fatigue, CSRS, Type B) to the four psychiatric symptoms (CSRS, Type A), the prevalence of four psychiatric symptoms (CSRS, Type A) was still significantly greater than the most prevalent combinations of five symptoms (when adding Cognitive deficits, 8%, 95%CI: 6.3-11.1) or six symptoms (when adding Cognitive Deficits and Fatigue, 4%, 95%CI: 2.8-6.3) at $P = 0.003$, $P < 0.001$, respectively), showing that the prevalence of CSRS, Type A is significantly greater than all combinations of symptoms studied. Thus, these results endorse our two-tailed hypothesis, confirming that one tail of the two (CSRS, Type A) is significant. These findings suggest that the CSRS, Type A is applicable for the general population without direct association with the neuropsychiatric part of long-Covid (CSRS, Type B), and that it is not necessarily related to the viral infection and its suspected residuals. Bonferroni correction for multiple comparisons was conducted and the results were significant at $P < 0.01$.

As shown in Table 2, more people reported the combination of all 4 psychiatric symptoms (CSRS, Type A) than the combinations of fewer symptoms.

In further analyses to detect subpopulations at risk, a MANCOVA was conducted with four continents, five age groups and three types of gender as independent variables, while keeping the 4 psychiatric components of the CSRS, Type A as dependent variables, controlling for COVID-infected/recovered *vs* non infected/recovered individuals as a covariate. A three-way interaction was found: Continent × age × gender [$F(14,925) = 1.747$, $P < 0.05$ with observed power of 0.903] (Figures 1 and 2). The covariate did not significantly add to the explained variance. Follow up analyses showed that the sources of the three-way interaction were threefold, consistently over the 4 dependent variables (Anxiety, Depression, Stress and PTSD, CSRS, Type A): (1) In North America, participants aged < 50 years old, self-identifying as non-binary, reported significantly higher scores than both women and men ($P < 0.05$); (2) Women at young ages (< 40 years old) in North America scored higher compared to men and women in other continents and other ages; and (3) In North America, women at young ages (< 40 years old) and participants self-identifying as non-binary gender, aged < 50, scored above the clinical cutoff points, although women's scores were significantly lower ($P < 0.05$) than the scores of the non-binary gender at these young ages.

The sources of the three-way interaction, which in turn correspond to identified populations at risk, were confirmed by linear regression analyses, which do not require an assumption of variables' normal distributions.

Specifically, Anxiety score was negatively associated with being a man [b = -1.42 (-2.22, -0.62)] and positively associated with non-binary gender [b = 3.81 (1.53, 6.10)], negatively associated with age groups 50-60 [b = -1.36 (-2.56, -0.15)] and > 60 [b = -3.06 (-4.59, -1.53)] and living in Australia [b = -2.96 (-3.85, -2.07)] or the Middle-East [b=-2.06 (-3.84, -1.36)] compared to North America.

Depression score was negatively associated with being a man [b = -1.57 (-2.42, -0.72)] and positively associated with non-binary gender [b = 5.08 (2.65, 7.51)] while negatively associated with age group > 60 [b = -2.89 (4.52, 1.26)] and living in Australia [b = -2.01 (-2.96, -1.06)] or the Middle-East [b = -2.97 (-4.28, -1.64)] compared to North America.

Stress symptoms score was negatively associated with being a man [b = -2.02 (-3.15, -0.88)] and positively associated with non-binary gender [b = 4.65 (1.40, 7.90)], negatively associated with age groups 50-60 [b = -2.12 (-3.84, -0.40)] and > 60 [b = -5.33 (-7.51, -3.16)] and living in Australia [b = -3.24 (-4.51, -3.98)] or the Middle East [b = -4.49 (-6.25, -2.72)] compared to North America.

PTSD score was negatively associated with being a man [b = -2.89 (-4.09, -1.70)] and positively associated with non-binary gender [b = 6.34 (2.92, 9.75)], negatively associated with older age group > 60 [b = -4.86 (-7.15, -2.57)] and living in Australia [b = -3.53 (-4.86, -2.20)], Europe [b = -3.43 (-6.02, -0.85)] or the Middle East [b = -4.44 (-6.29, -2.59)] compared to North America.

DISCUSSION

The results of this study show that the prevalence of 4 symptoms, combining anxiety, depression, stress symptoms and PTSD, was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups (> 18 years old), and gender. This supports the transdiagnostic hypothesis embedded in the CSRS (Type A) and shows its clinical value as a future potential diagnosis spanning 4 conventional diagnostic categories.

Table 1 Correlation coefficients between all six dependent variables

Correlation table	PHQ	PSS	ITQ	GAD	Cognitive	Fatigue
PHQ	1	0.79[a]	0.74[a]	0.80[a]	0.4[a]	0.24[a]
PSS	0.79[a]	1	0.74[a]	0.79[a]	0.3[a]	0.25[a]
ITQ	0.74[a]	0.74	1	0.71[a]	0.34[a]	0.31[a]
GAD	0.80[a]	0.79[a]	0.71	1	0.311	0.25[a]
Cognitive	0.4[a]	0.3[a]	0.34[a]	0.311[a]	1	0.30[a]
Fatigue	0.24[a]	0.25[a]	0.31[a]	0.25[a]	0.30[a]	1

[a]$P < 0.001$.

As shown in Table 1, all components of the CSRS type A and type B are significantly correlated. PHQ: Patient Health Questionnaire; PSS: Perceived Stress Scale; ITQ: International Trauma Questionnaire; GAD: Generalized Anxiety Disorder.

Table 2 All combinations of symptoms reported

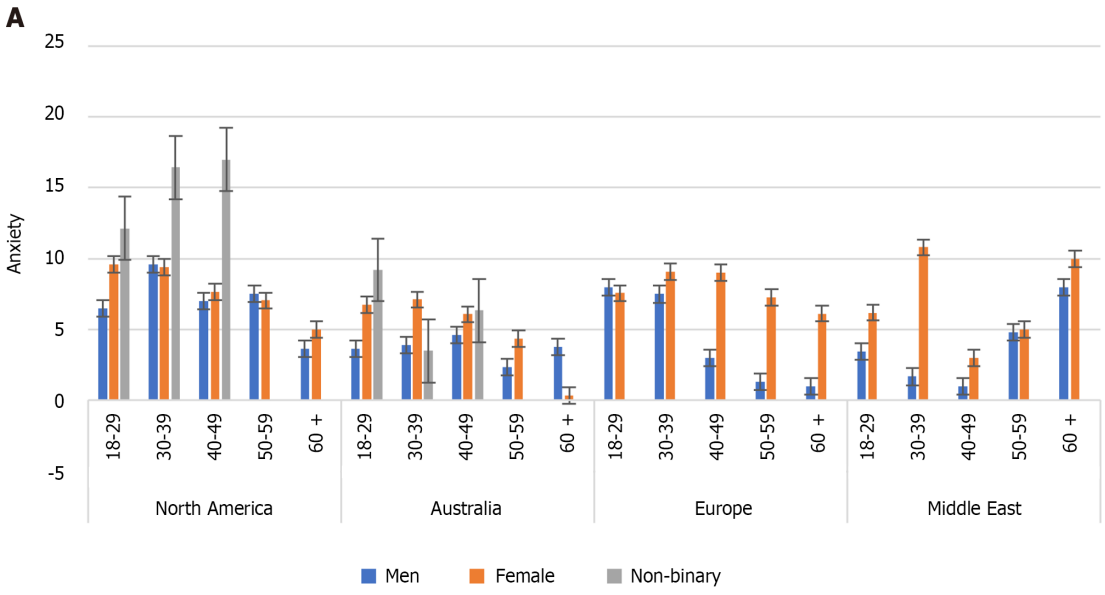
General population	Percentage
Combination	
None	10
Stress	20
Depression	0
Anxiety	3
PTSD	2
Stress + depression	0
Anxiety + depression	0
PTSD + depression	0
Stress + anxiety	6
Stress + PTSD	4
Anxiety + PTSD	1
Stress + depression + anxiety	3
Stress+ depression + PTSD	1
Stress + anxiety + PTSD	13
Depression+ anxiety + PTSD	0
All	31

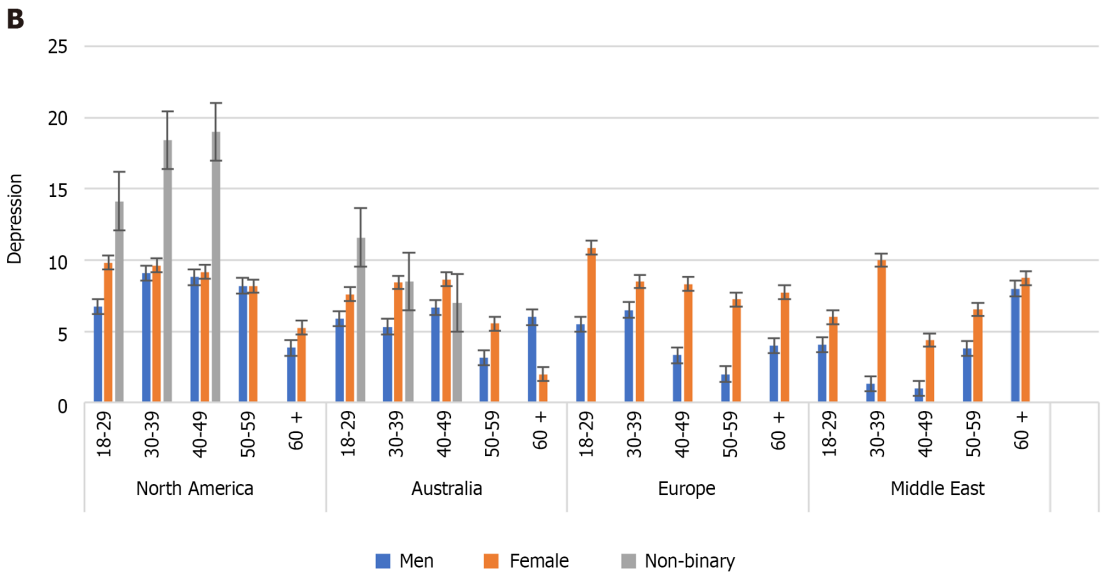
PTSD: Post-traumatic stress disorder.

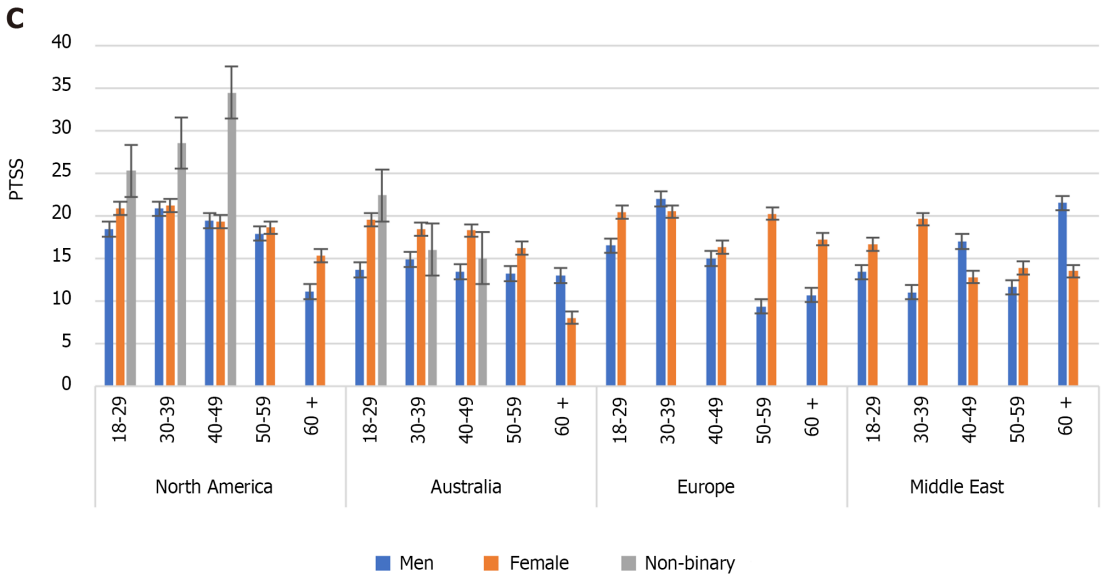
The results show that the CSRS is sensitive to demographic variability and especially to the differences between cultures, locations and gender types. The overall analyses confirm the transdiagnostic hypothesis by showing that over 4 continents and gender types more symptoms were significantly more prevalent than fewer symptoms.

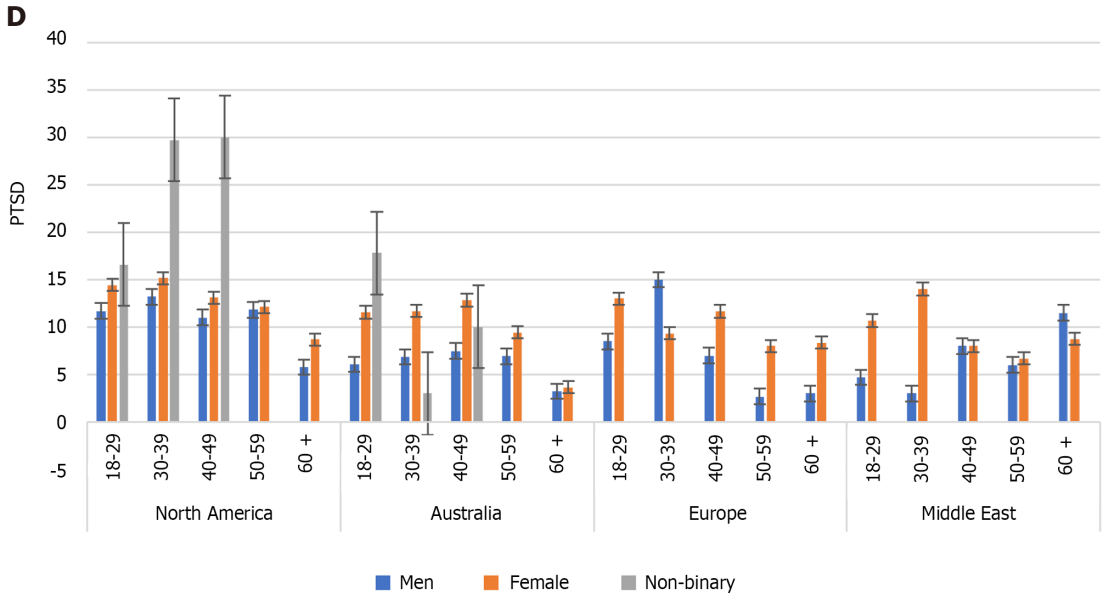
One identified source for the significant three-way interaction found in this study (age × gender × continent), and confirmed by regression analyses showed, that the group that self-identified as non-binary gender scored significantly higher on all four psychiatric symptoms of the CSRS at young ages (< 40 years old) in North America compared to (self-identified) women and (self-identified) men located in the 4 continents studied, and to other ages across the adult life span. These results show a combined mental health risk factor, suggesting that the CSRS, Type A is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations.

In the scientific literature, identifying as non-binary at a young age has been recognized as a risk factor for increased mental health problems compared to other age groups and to other gender identities including other types on the gender identity spectrum such as the transgender identity[38,39]. The reduced affective wellbeing of those who identify as non-binary gender have been documented in research and theoretical conceptualizations[38,40,41]. To describe the unique type of distress that non-binary gender individuals might experience the term "gender minorities stress" was suggested


A
Anxiety
25
20
15
10
5
0
-5
18-29
30-39
40-49
50-59
60 +
North America
Australia
Europe
Middle East
Men
Female
Non-binary


B
Depression
25
20
15
10
5
0
18-29
30-39
40-49
50-59
60 +
North America
Australia
Europe
Middle East
Men
Female
Non-binary


C
PTSS
40
35
30
25
20
15
10
5
0
18-29
30-39
40-49
50-59
60 +
North America
Australia
Europe
Middle East
Men
Female
Non-binary



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Figure 1 The measures assessing the four psychiatric features of the Complex Stress Reaction Syndrome (CSRS, Type A, mean ± SD). A: The Generalized Anxiety Disorder (anxiety measure); B: The Patient Health Questionnaire-8 (depression measure); C: The Perceived Stress Scale (perceived stress measure); D: The International Trauma Questionnaire (post-traumatic stress disorder measure).

[42]. We note that more conservative social views in continents other than North America may have inhibited people from identifying as non-binary and prevented an even larger magnitude of the non-binary gender stress reactivity in our findings. The emotional burden of this minority and its dramatic impact on this study's results attests to the extreme distress experienced by this sub-population.

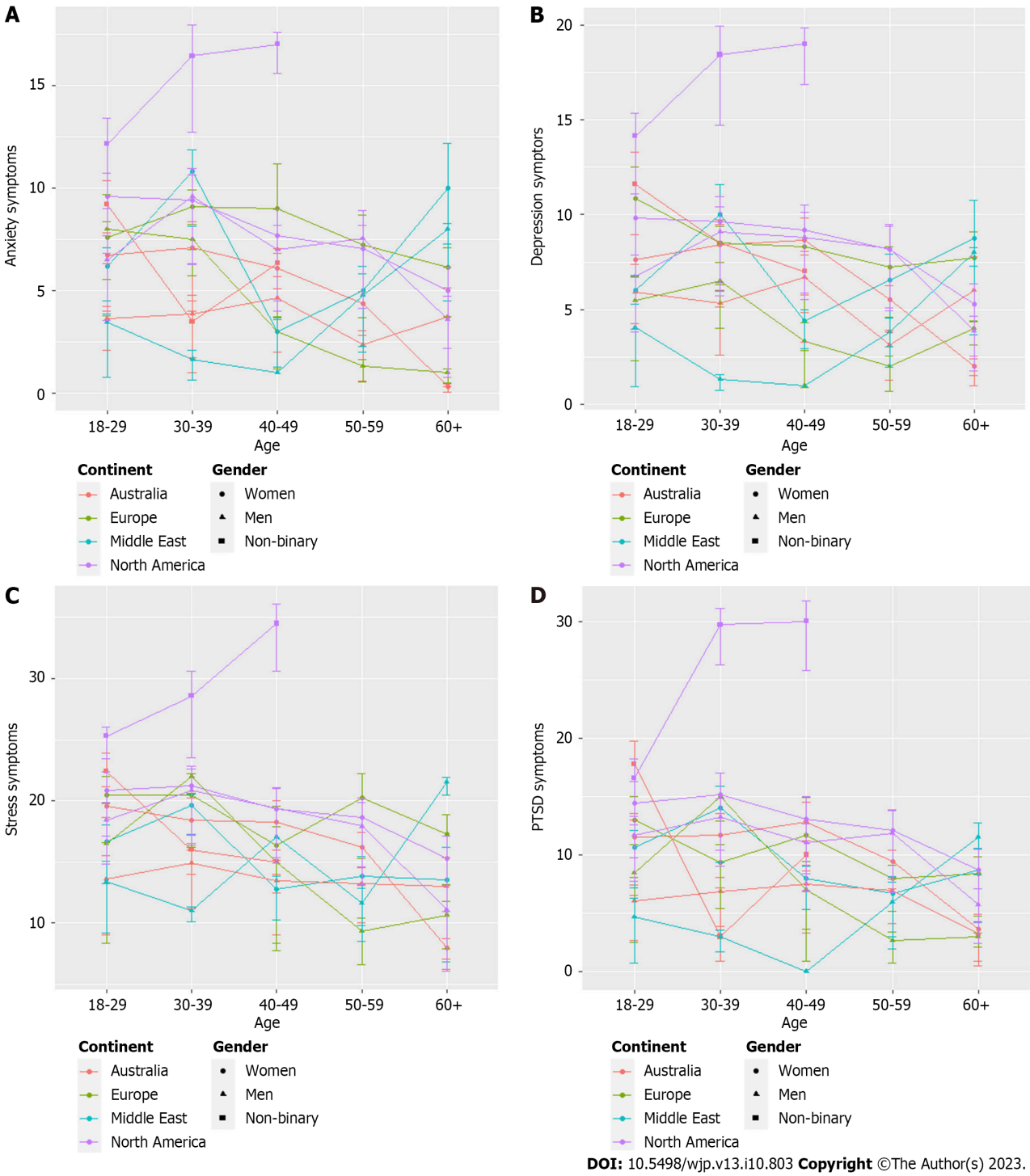
An additional source for the three-way interaction is related to another sub-population at risk which scored above the clinical cutoffs of all the four types of symptomatology included in the CSRS, Type A, young age groups identifying as a woman in North America. Being a woman at young age has been reported as a risk factor long before the COVID-19 outbreak[43,44], during the COVID-19 pandemic[45] and in the post-COVID era[46] in very large, epidemiological studies. Thus, our results show the sensitivity of the CSRS, Type A in measuring a specific stress reactivity spanning several conventional categories in both minoritized and majority subpopulations.

In this study, the psychiatric pattern of symptoms (CSRS, Type A) was similar in infected/recovered SARS-CoV-2 patients and in the non-infected population, suggesting that the CSRS, Type A is sensitive to a clinical picture in daily life, beyond its relevance to catastrophes, including the COVID-19 pandemic[16]. The neuropsychiatric part of the CSRS relating to neuropsychiatric components of the long-COVID syndrome (CSRS, Type B), did not add to the explained variance and the same pattern of results was found in infected/recovered individuals. These results show that the psychiatric part of the CSRS (Type A), when controlling for infected-non infected conditions, is the type of CSRS which is sensitive to at-risk sub-populations. In accordance with a current debate, this study also suggests that the long-COVID syndrome is a too broad diagnostic category in neuropsychiatry, resulting in recent contradictory results[47,48]. Thus, the CSRS shows relevance for daily life stressors, beyond the pandemic situation and not as a mandatory result of the viral infection.

Thus, the CSRS, Type A represents a unique transdiagnostic clinical picture combining symptomatology of affective disorders with stress reactivity[16,26,31]. The prevalence of affective disorders spans a wide range of symptomatology, with dramatic cross-cultural differences[49]. Reports on prevalence of stress reactions are also present across a wide range mental disorders[50]. Furthermore, earlier studies reported that at-risk populations do not necessarily meet the full criteria of affective disorders and stress reactivity categories[40,44]. As it arises from the current findings, and according to our previous arguments[26], the CSRS, Type A identifies, and is sensitive to individual differences in stress reactivity and reduced positive affectivity, within a transdiagnostic spectrum.

The correlative design of this study is the most appropriate for the current stage of CSRS development as only after assuring the face validity of the hypothesized syndrome by empirical data, including its highly associated symptoms, a follow up design on etiological questions related to more causal assumptions may be investigated. In fact, to show that any transdiagnostic hypothesis is related to associations between symptoms spanning several traditional categories, a correlative design should be employed.

As the aim of this research is primarily transdiagnostic, its correlative design affords testing the relationship and extent of association between a given number of variables (symptoms) spanning traditional classifications without meeting them in full. This type of design also allows testing whether a correlative combination of more symptoms is more prevalent than a combination of fewer symptoms from a given number of hypothesized variables, in a given hypothesized combination.



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Figure 2 Three-way interactions between continents, age groups and gender identifying the sub-populations at risk by the four psychiatric features of the Complex Stress Reaction Syndrome (CSRS, Type A). A: Three-way-interaction for the Generalized Anxiety Disorder (anxiety measure); B: Three-way-interaction for the Patient Health Questionnaire-8 (depression measure); C: Three-way-interaction for the Perceived Stress Scale (perceived stress measure); D: Three-way-interaction for the International Trauma Questionnaire (post-traumatic stress disorder measure).

The correlative design used in this study aimed also to show the sensitivity of CSRS to populations at risk who score beyond the clinical cutoff of the measures used. As such, the study also aimed to investigate the generalizability of the CSRS across continents, gender types and age-groups. This required comparisons between continents, gender types and age-groups. Thus, a correlative design and its aligned conclusion on associations between symptoms as related to demographic factors, may be derived even when employing statistical comparisons between independent (demographic, in this case) variables, and their assumed related "causal" impact on the dependent (CSRS, Type A) variables. The advantage of this approach and conclusions regarding association between independent (demographic) and dependent (CSRS, Type A) variables is threefold from both scientific and clinical perspectives: (1) It shows the generalizability of the CSRS; (2) It shows the CSRS, Type A as clinically essential for the identification of populations at risk, suggesting that the CSRS, Type A is sensitive to a unique transdiagnostic mental health condition; and (3) It includes a suspected indication

to treat. Furthermore, the results of the analysis of variance were confirmed by significant associations between the same demographic variables and the most prevalent combination of symptoms (CSRS, Type A) in linear regression analyses. Thus, the same populations at risk, as well as the sensitivity of the CSRS to these populations, are apparent in the results of this study.

The limitations of this study lie in the sampling methods utilized, which used convenience sampling[51]. This type of convenience online sampling became very popular and legitimate during the pandemic, although very large samples have been criticized before and after the pandemic[52,53]. Additional limitations include the use of self-report measures (symptoms) and not diagnostic interviews (signs), and the possible bias towards samples who are computer literate. However, in our binational research[26], we combined the methodology of representative sampling (Israel) with convenience sampling (Italy) and found similar results, although employing two different sampling methodologies, supporting the validity of the online convenience sampling. Yet to come, international studies with representative sampling, are warranted for further support of the CSRS, Type A validity and its clinical value.

This current international study emphasizes the importance of transdiagnostic approaches for clinical identification of individual differences and sub-populations at risk that do not meet the full criteria of any traditional category. This will afford the development of more accurate prevention and treatment for those with emotional needs who remain without a clear diagnosis and proper clinical care.

CONCLUSION

This study shows a global new picture of the indication to treat derived from (1) The different populations included from around the globe; and (2) Allowing a transdiagnostic perspective. Although the categorical model of diseases remains largely used worldwide[26], the future will tell if transdiagnostic categories will be part of the next revisions of the DSM and ICD conventional systems to facilitate a resolution of the crisis in the field of psychiatry[1]. Indeed, a transdiagnostic approach recognizes the inherent complexity and heterogeneity of mental disorders by focusing on shared underlying dimensions rather than rigid diagnostic categories. This allows for a more nuanced understanding of psychopathology and better captures the overlapping symptomatology often observed across different disorders. Hence, future international transdiagnostic clinical research is warranted. To support psychiatrists in their clinical practice, future research may utilize transdiagnostic approaches to classify patients who show a mixed clinical picture when applied in face-to-face clinical meetings (signs) compared to remote self-scoring (symptoms) by the same patients.

ARTICLE HIGHLIGHTS

Research background

The debate regarding diagnostic classification systems in psychiatry (categorial *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions.

Research motivation

We previously found a unique pattern of stress reaction in a study executed during the coronavirus disease 2019 pandemic using large representative samples in two countries, and termed it the Complex Stress Reaction Syndrome (CSRS). In the current international study, in four continents, using six languages we aimed to investigate the generalization of the CSRS and its sensitivity to populations at risk.

Research objectives

We aimed to investigate CSRS, Type A [psychiatric symptoms, spanning anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)], with or without long-COVID residuals (CSRS, Type B, neuropsychiatric symptoms spanning cognitive deficits and fatigue, excluding systemic symptoms). Our two-tailed hypothesis was that CSRS is a condition related to an unrecognized type of stress reaction in daily life in the general population (Type A) or that it is related to the severe acute respiratory syndrome coronavirus 2 infection and its long-COVID residuals (Type B).

Research methods

Media-supported study using the Qualtrics platform.

Research results

The results of the Proportion Analyses showed that the prevalence of 4 symptoms spanning anxiety, depression, stress symptoms, and PTSD was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups, and gender (CSRS, Type A). Further analyses identified two populations at risk: (1) Individuals that self-identified as non-binary gender; and (2) Women at young ages (< 40 years old) in North America.

Research conclusions

These results show a combined mental health risk factor related to stress reactivity, suggesting that the CSRS is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the

transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

Research perspectives

A follow-up international study to investigate whether the condition of multiplicity of stressors is the etiological source for developing the CSRS, Type A clinical status, is warranted.

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FOOTNOTES

Author contributions: Goldstein Ferber S developed the CSRS conceptualization and was the leading author; Rossi R supervised the statistical analyses and data collection; All the other authors contributed to the study and the last version of this paper.

Institutional review board statement: IRB approvals for this international study were provided by The Johns Hopkins University, Baltimore, Maryland, USA, and by Bar Ilan University, Ramat-Gan, Israel. The study survey used the Qualtrics platform (Qualtrics, Provo, Utah, USA) for data collection.

Informed consent statement: All study participants provided online informed consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The study data are available upon request.

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REVIEW

Management of acute carbamazepine poisoning: A narrative review

Luan Wang, Yang Wang, Ruo-Ying Zhang, Yao Wang, Wei Liang, Tie-Gang Li

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Abstract

Standard management protocols are lacking and specific antidotes are unavailable for acute carbamazepine (CBZ) poisoning. The objective of this review is to provide currently available information on acute CBZ poisoning, including its management, by describing and summarizing various therapeutic methods for its treatment according to previously published studies. Several treatment methods for CBZ poisoning will be briefly introduced, their advantages and disadvantages will be analyzed and compared, and suggestions for the clinical treatment of CBZ poisoning will be provided. A literature search was performed in various English and Chinese databases. In addition, the reference lists of identified articles were screened for additional relevant studies, including non-indexed reports. Non-peer-reviewed sources were also included. In the present review, 154 articles met the inclusion criteria including case reports, case series, descriptive cohorts, pharmacokinetic studies, and *in vitro* studies. Data on 67 patients, including 4 fatalities, were reviewed. Based on the summary of cases reported in the included articles, the cure rate of CBZ poisoning after symptomatic treatment was 82% and the efficiency of hemoperfusion was 58.2%. Based on the literature review, CBZ is moderately dialyzable and the recommendation for CBZ poisoning is supportive management and gastric lavage. In severe cases, extracorporeal treatment is recommended, with hemodialysis as the first choice.

Key Words: Carbamazepine poisoning; Management; Activated charcoal therapy; Extracorporeal treatment; Intravenous lipid emulsion

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Core Tip: There is no effective Antidote and standard treatment management for carbamazepine (CBZ) poisoning. This paper describes and summarizes the detailed clinical evidence of the treatment and management of CBZ poisoning, including gastric lavage and activated carbon therapy, hemoplavage, hemodialysis, continuous renal replacement treatment and plasmapheresis. Finally, this paper also provides the lipid resuscitation therapy to provide help for clinical treatment. In general, this paper summarized the results of CBZ poisoning related research, and provided the best plan for CBZ poisoning treatment.

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INTRODUCTION

Carbamazepine (CBZ) was discovered by Walter Schindler in 1953 and first utilized to treat partial tonic-clonic seizures in the United States in 1974[1]. Currently, CBZ is widely used for the treatment of epilepsy and peripheral neuralgia. Broad indications for the use and widespread availability of CBZ increase the risk of overdose, and CBZ intoxication accounts for a large proportion of life-threatening cases of anticonvulsant toxicity[2-4]. A systematic review of CBZ was published in 2014 by the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup that provides recommendations for the use of extracorporeal treatments (ECTRs) in cases of CBZ poisoning[5]. Currently, standard management protocols are lacking and specific antidotes for acute CBZ poisoning are unavailable; thus, we reviewed and summarized the various therapeutic methods for the treatment of CBZ poisoning described in previous studies. Our goal was to provide currently available information on acute CBZ poisoning, including its management. We believe this paper will help clinicians effectively manage patients suffering from CBZ intoxication.

METHODOLOGY

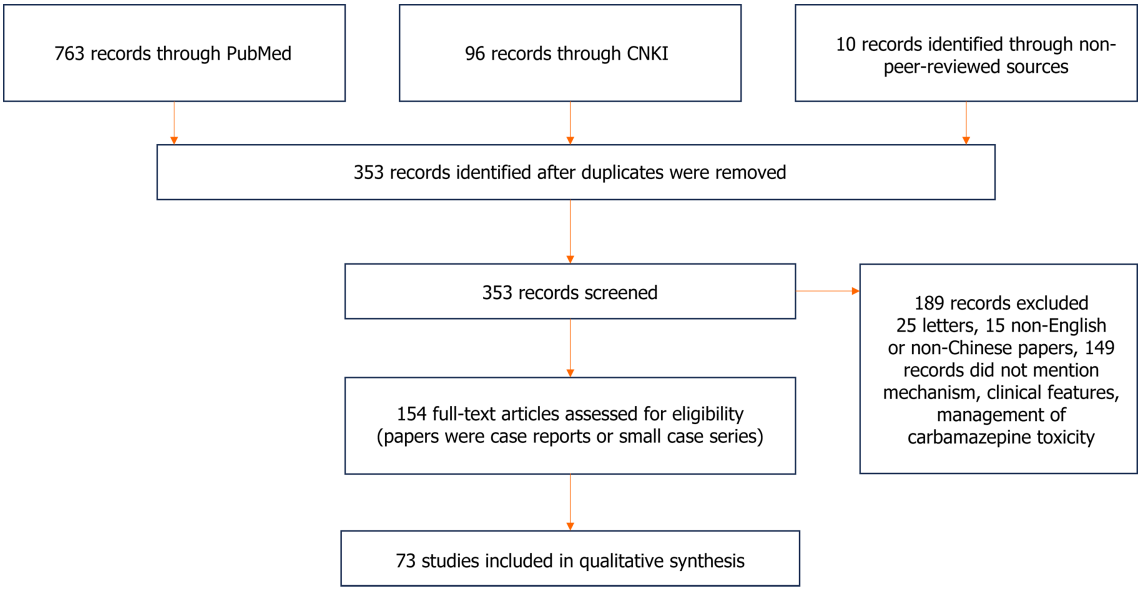
A literature search was performed in the following databases: PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wanfang. The search strategy, in English and Chinese, used the terms "acute" and "carbamazepine" in combination with the keywords "poisoning", "intoxication", "toxication", "toxicity", "overdose", and "overdosage". These search terms identified 861 records. In addition, the reference lists of the identified articles were screened for additional relevant studies, and these additional searches added three records. Non-peer-reviewed sources were also searched, including books and Internet resources, which yielded 10 records. A total of 874 records were found, which were screened based on title, author, journal name, and publication date for repeatability and relevance. We excluded papers that were duplicates, non-English or non-Chinese papers, letters to editors, and those not referring specifically to the mechanisms of action, clinical features, and management of CBZ toxicity in humans. Finally, 154 articles were considered eligible for review. The majority of papers were case reports or small case series. The literature selection process is described in Figure 1.

PHARMACOLOGY

CBZ is an iminostilbene derivative that is structurally similar to tricyclic antidepressants and is mainly used as a potent first-line agent to treat epilepsy, including simple partial, complex partial, and general tonic-clonic seizures[6,7]. The therapeutic effects of CBZ have also been proven for the treatment of neuropathic pain, especially prosopalgia, central diabetes insipidus, attention-deficit/hyperactivity disorder, and bipolar disorder. CBZ is thought to exert its anticonvulsant effects by blocking presynaptic voltage-gated sodium channels in the central nervous system (CNS), which further prevents the release of glutamate and similar neurotransmitters, ultimately inhibiting high-frequency epileptic foci.

CBZ has a molecular weight of 236 Da and high protein binding affinity (70%-80%) for both albumin and alpha-1-acid glycoprotein. This percentage does not markedly decline, even in cases of overdose[8]. CBZ is highly lipophilic, a property that allows it to be rapidly distributed after ingestion with a moderately large volume of distribution ranging between 0.8 L/kg and 1.4 L/kg. Thus, at therapeutic doses, the immediate-release tablets and controlled-release formulation of CBZ have peak serum concentrations at approximately 6-8 h and 12-24 h post-ingestion, respectively[9-11]. However, following overdose, peak concentrations may be delayed up to 106 h[12] due to the anticholinergic properties of CBZ, which are responsible for decreased gastrointestinal (GI) motility and delayed and prolonged absorption[10,13].

CBZ metabolism predominantly and extensively occurs in the liver by epoxidation and hydroxylation reactions through the cytochrome P450 system. Only 1%–3% of the drug is not metabolized and excreted through the kidney. CBZ-



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Figure 1 Flow diagram of the literature search.

10,11-epoxide is the primary active metabolite and equally produces antiepileptic and toxic effects based on its capacity to form covalent protein conjugates[14,15]. CBZ-10,11-epoxide blood concentrations vary substantially between individuals, ranging from 15% to 55% of CBZ levels in adults and from 5% to 81% of CBZ levels in children[11]. CBZ metabolism is complicated because both normal metabolism and autoinduction of metabolism occur with chronic use.

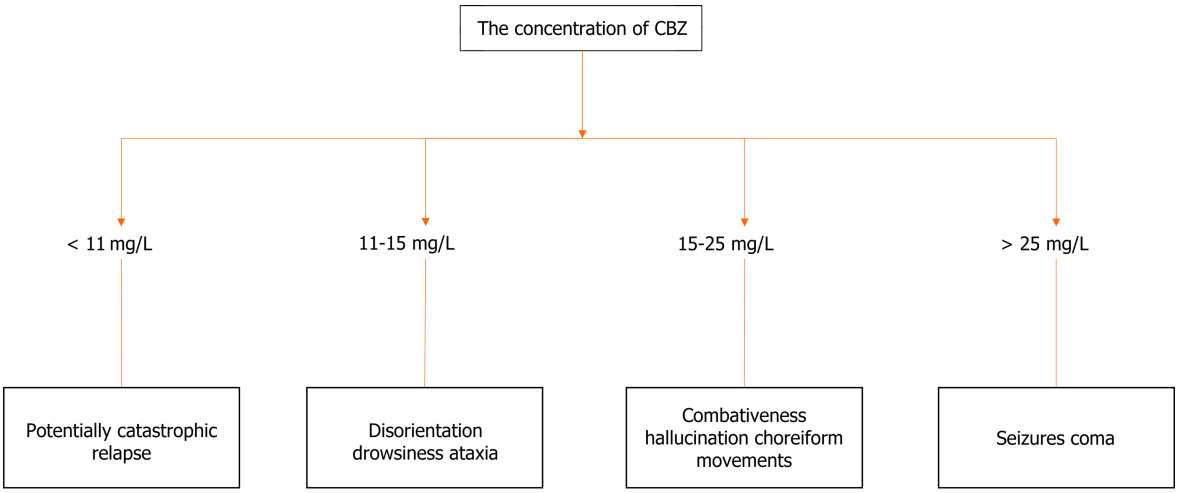
There is wide interindividual variability in the pharmacokinetics of CBZ, as well as general adaptation[16]. CBZ is eliminated according to zero-order kinetics (*i.e.* a constant amount of drug is eliminated per unit time) in the case of elevated plasma drug levels, as seen in overdose; however, a delay in CBZ elimination occurs when no intervention is available[16]. The reported biological half-life of the initial dose of CBZ is 25-65 h, but is shortened to 12-17 h in chronically treated epileptic patients due to self-induction[17]. Nevertheless, the half-life is apparently much longer after excessive dosing and the use of controlled-release preparations[1,12], likely reflecting delayed or continuous absorption, impaired elimination, or a combination of both.

OVERVIEW OF CBZ POISONING

Toxicity from CBZ overdose was first described by Guntelberg in 1967[18]. CBZ intoxication increasingly accounts for a large proportion of life-threatening cases among anticonvulsant poisonings[2,3]. A total of 3734 toxic exposures to CBZ were reported in 2014 by the American Association of Poison Control Centers. Of these, 1880 were isolated ingestions. There were no deaths, but 62 cases were life-threatening or severely disabling due to the significant toxicity[19].

Although the toxic concentration of CBZ in patients is not completely consistent with clinical manifestations of toxicity, doctors often initially treat patients based on the patient's clinical status. However, serum CBZ concentration is a practical method used to confirm clinical exposure, and severe intoxication occurs at serum levels > 20 mg/L [therapeutic index range: 4-12 mg/L (17-51 μmol/L)][20]. Serum CBZ levels > 40 mg/L are generally predictive of severe toxicity[21], which potentially occurs at a lower concentration[22], especially in children[23-25], and tends to be associated with an increased risk of seizure, coma, respiratory depression, and cardiotoxicity[26,27]. In addition, the pharmacologically active metabolite of CBZ, CBZ-10,11-epoxide, contributes to the risk of toxicity[28,29]. Based on the circulating level of CBZ in blood, the effects of CBZ on the CNS can be classified into four stages: (1) Seizures and coma at levels > 25 mg/L; (2) Combativeness, hallucinations, and choreiform movements at levels of 15-25 mg/L; (3) Disorientation, drowsiness, and ataxia at levels of 11-15 mg/L; and (4) Potentially catastrophic relapse at levels < 11 mg/L[30]. The duration and severity of these stages are variable and depend upon the magnitude of the overdose[31]. The detailed clinical symptoms corresponding to the toxic dose are described in Figure 2.

Toxicity usually occurs within 1-3 h after ingestion, but may be prolonged due to the delayed and erratic absorption of CBZ[32,33]. A wide diversity of clinical manifestations such as neurologic, respiratory, and cardiac findings can be seen in CBZ poisoning[22,34]. CBZ intoxication primarily manifests as CNS symptoms including nystagmus, movement disorders, disturbance of consciousness, altered mental status ranging from drowsiness to coma, and convulsions[35-39]. Seizures are not uncommon, occurring in 11%-18% of overdose cases[40,41]. Respiratory depression, a common manifestation of severe overdose, may delineate the severity of toxicity in the respiratory system and may be complicated by concomitant aspiration. Myocardial depression, sinus tachycardia, hemodynamic instability hypotension, and cardiac conduction disturbances are characteristics of CBZ cardiotoxicity. Some rare electrocardiogram (ECG) abnormalities may also occur such as atrioventricular block, QRS interval prolongation, QTc (corrected QT time in ECG) prolongation (> 420



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Figure 2 Toxic dose and clinical manifestations of carbamazepine according to blood concentration. CBZ: Carbamazepine.

ms), bundle branch block, Brugada-type patterns, and premature ventricular contractions[42,43]. Death, though very uncommon (approximately 2% of cases), generally results from cardiovascular toxicity[44,45]. An overall mortality rate of 13% was documented and reported in a cohort study of 427 patients with CBZ intoxication, with an average CBZ intake in lethal cases of 23.6 g[22]. Refractory cardiovascular toxicity has also been reported[46,47].

MANAGEMENT OF ACUTE POISONING

In clinical practice, doctors initially treat patients based on their clinical symptoms, and supportive care plays a key role at this stage. For example, seizures are treated with benzodiazepines[48], hypotension is treated with vasopressors, and endotracheal intubation is used for patients with respiratory insufficiency. GI decontamination techniques such as gastric lavage (GL) and single-dose activated charcoal (AC) (SDAC) can be applied if patients are administered care within 1-2 h after ingestion without contraindications[49]. However, CBZ metabolism and distribution are complicated, and specific life-saving antidotes for CBZ poisoning are unavailable. Several modalities have been proposed to enhance CBZ clearance in patients with severe or life-threatening ingestion, including multiple-dose AC (MDAC), ECTRs, and lipid resuscitation therapy (LRT)[50].

Supportive care

Application of appropriate supportive care is adequate to deal with the vast majority of CBZ intoxication cases. Supportive care may involve airway protection with endotracheal intubation, treatment of seizures with benzodiazepines, and correction of hypotension with fluid challenges and vasopressors, if needed. The use of hypertonic sodium bicarbonate is indicated if ECG findings (QRS duration exceeding 100 msec) show that the sodium channel is blocked.

Serum CBZ concentrations in an acute overdose should be monitored serially (typically every 4-6 h) until a definitive downward trend is observed and the patient is improving clinically[51,52]. Continuous monitoring of serum CBZ concentrations in patients is necessary, especially in those with severe poisoning. These patients are likely to deteriorate after the initial improvement of clinical symptoms or develop a delayed toxic reaction due to a rebound effect (*i.e.* sudden rise in serum drug concentration following intermittent treatment due to drug redistribution from tissue to serum[53]) or sustained increase in serum concentration.

Patients with significant CNS depression may lose protective airway reflexes and should be intubated, particularly due to their lower seizure threshold. Short-acting neuromuscular blocking agents (*e.g.*, succinylcholine) are preferable so subsequent seizure activity is not masked. Induction agents with gamma-amino butyric acid agonist activity (*e.g.*, midazolam) may be preferable, depending on the patient's hemodynamic status.

Hypotension is initially treated with isotonic crystalloid. Caution should be exercised in patients at risk of volume overload, such as those with underlying heart disease or CBZ-induced myocardial dysfunction. Direct-acting vasopressors are used if intravenous fluids fail to correct the hypotension.

Sodium channel blockade may cause QRS interval prolongation, which, in other poisonings, has been shown to predispose patients to ventricular arrhythmias[54,55]. QRS prolongation due to CBZ toxicity is treated with sodium bicarbonate. Currently, there are no clearly established treatment thresholds based on QRS duration or dosing guidelines or evidence regarding the preferred method of administering sodium bicarbonate with respect to boluses, infusions, or treatment duration[56]. The proposed methods of administration are for patients with QRS intervals longer than 110 ms, particularly those with hypotension, and include boluses of a 1 mEq per 1 mL (8.4%) solution at a quantity of 1-2 mEq/kg to obtain a serum pH of 7.45-7.55 and an infusion of 150 mEq mixed with 1 L of 5% dextrose in water at a rate to maintain

that pH[54]. Continuous cardiac monitoring of patients with a 12-lead ECG is simultaneously needed. Volume overload, hypokalemia, hypernatremia, and metabolic alkalosis may result from prolonged bicarbonate infusions, and clinical and laboratory parameters must be closely followed to avoid these complications.

GL

GL has been routinely used to manage cases of poisoning for more than 200 years. However, GL carries significant risks, which, given its questionable clinical benefit, usually outweigh arguments in favor of its use; thus, it is not recommended for routine GI decontamination[57]. GL works by eliminating poison remaining in the GI tract and should be considered based on the time elapsed from oral ingestion to admission to the emergency department. In cases of suspected CBZ intoxication, prior to the determination of the current plasma concentration of CBZ, it is imperative to remove undigested tablets through GL to further reduce GI absorption. This one simple measure may be particularly helpful for CBZ intoxication given its anticholinergic effects on the GI tract that would delay gastric emptying[58]. However, there is less conclusive evidence showing that GL has clear effects on CBZ poisoning[59,60]. As noted in a position statement related to GL use, GL should not be considered unless a potentially life-threatening amount of a poison is ingested by the patient, and this approach should be initiated within 60 min of ingestion[61]. Nevertheless, the clinical benefit has not been confirmed in controlled studies. Moreover, GL is not appropriate for all patients, and not all patients can benefit from GL. GL is contraindicated in patients who have impaired consciousness, recent surgery, no protection of the airway, risk of GI bleeding and perforation, and potentially increased risk and severity of aspiration[57]. The major complications of GL include perforation of the esophagus and stomach, pulmonary aspiration, and aspiration pneumonia[62].

MDAC

AC therapy is still the most frequently employed method of GI decontamination for acute drug overdoses in developed countries. With a highly developed internal pore structure, the tremendous surface area of AC permits the adsorption of drugs and toxins in the GI tract within minutes of contact, which reduces their systemic absorption and subsequent toxicity and enhances their elimination[63]. AC therapy involves SDAC and MDAC, which indicates scheduled administration of more than two small doses of AC.

MDAC should only be considered if a patient has ingested a life-threatening amount of CBZ. MDAC therapy is effective in poisoning due to three distinct mechanisms: (1) Reducing ongoing absorption of extended or delayed-release formulations remaining in the gut[49]; (2) Interfering with enterohepatic and enterogastric circulation of drugs[64-66]; and (3) Promoting the diffusion of drugs from circulation into the gut lumen and trapping them there to be discharged later in the excrement (this process is sometimes called "GI dialysis")[67].

The "routine" use of MDAC has not been shown to reduce morbidity and mortality in poisoned patients in controlled clinical trials. However, evidence from animal and volunteer studies, as well as poisoning cases, indicates that MDAC therapy significantly enhances total body clearance and shortens the half-life of CBZ[33,68-71]. Mittag *et al*[19] recently reported a case of CBZ overdose in which the patient was treated with AC (1 g/kg body weight); his CBZ concentration dropped from the initial value of 41.5 mg/L to approximately 12 mg/L after 24 h. A randomized crossover study in 5 fasted volunteers performed by Neuvonen and Elonen[65] showed that the elimination of CBZ could be significantly enhanced by MDAC. In a study by Boldy *et al*[70] involving 15 patients with CBZ poisoning, researchers gave patients MDAC therapy and found that the mean half-life decreased to 8.6 ± 2.4 h and the mean total body clearance increased to 113 ± 44 mL/min. By comparison, the mean elimination half-life in another two groups of patients managed with supportive treatments only was approximately 19 h[8,72]; similar conclusions have been reached in other studies[73,74].

MDAC enhances the clearance of CBZ in the body and has been approved by the latest joint statement issued by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists [64]. The statement recommends that MDAC be considered only if a patient has ingested a life-threatening amount of CBZ. In addition, several conditions are considered contradictions including an unprotected airway, the presence of intestinal obstruction, and a GI tract not anatomically intact. Attention should be paid to prevent complications such as constipation, ileus, and aspiration pneumonia in an unprotected airway, although these occurrences are rare[75].

The efficacy of AC is inversely related to the time elapsed after the ingestion of toxic substances[42,76]; thus, administration of charcoal as soon as possible yields the best results. However, the considerably delayed absorption of drugs is often noted in cases of acute poisoning due to inhibition of gastric emptying and gut motility and the limited solubility of drugs, among other reasons[21,22]. Therefore, AC administration is apparently indicated if delayed or prolonged absorption is anticipated, even after a delay of 24-48 h[75].

There is no established optimal dosage regimen for AC; however, available data indicate a dose-response relationship: An AC: Drug ratio of 10:1 or higher is considered optimal for AC adsorption[77-79]. However, the efficacy of AC is influenced by many variables, making it difficult to administer the optimum dose[63]. Consequently, in practice, a fixed dose of 1 g/kg is generally recommended with the maximum amount not exceeding 50-70 g. A flexible dose of 0.25-1.0 g/kg is used for MDAC, and the dosing interval varies based on laboratory (*e.g.*, increasing blood concentrations) or clinical evidence for continuing drug absorption and ranges from 1 h to 4 h. Vomiting is an important factor to consider when substantial doses of AC are administered repeatedly. Continuous nasogastric infusion of AC or frequent administration of AC with smaller doses, at least following a large initial dose (50-100 g), may contribute to reduced vomiting[80,81]. In some cases, the combined use of antiemetics, such as metoclopramide or ondansetron, may have desirable effects.

ECTR

ECTR, also known as blood purification treatment, is a medical technology that removes poison from the blood by moving the blood from the patient into a purification device. ECTRs are classified based on their mechanism:

Hemodialysis (HD) and peritoneal dialysis act by diffusion; hemoperfusion (HP) acts by adsorption; hemofiltration acts by convection; and therapeutic plasma exchange acts by centrifugation[82,83]. Each technique has a potentially different role in eliminating poison from the body. Whatever modality is used, optimizing ECTR characteristics to achieve maximum removal of poison is crucial; for example, higher flow rates of blood and dialysate, filters with larger surface area, and longer duration of ECTR maximize poison removal[84].

According to the EXTRIP workgroup on the use of ECTR in CBZ poisoning, ECTRs are recommended for patients with significant or potentially significant clinical poisoning because they are preferable interventions for rapidly and substantially removing CBZ[5]. Even when considering its weaknesses, such as high risks, high costs, and relative uncertainty, ECTR is generally considered by the workgroup to be worth implementing in patients with severe CBZ poisoning (as manifested by signs such as multiple refractory seizures, hemodynamic instability requiring vasopressors, or life-threatening dysrhythmias). ECTR can prevent the worsening of CBZ poisoning symptoms such as severe hypotension, as well as comatose complications associated with chronic shortness of breath such as ventilator-associated pneumonia and pulmonary emboli[5]. In addition, ECTR is expected by most participants in the workgroup to be a potentially cost-saving technique by minimizing the mechanical ventilation period and residence time in the intensive care unit (ICU), ultimately reducing ICU-related costs[5]. Whether and when to initiate ECTR should be primarily based on clinical symptoms and signs, rather than serum CBZ concentrations, although more severe toxicity apparently occurs when CBZ concentrations are > 40 mg/L[21,85]. The optimal duration of extracorporeal removal should be adjusted to the patient's clinical condition and CBZ levels. Furthermore, the continuous and regular monitoring of CBZ serum concentrations after ECTR is essential, as concentrations may rebound[86]. If concentrations rebound to threatening levels or if there is a recurrence of toxic symptoms, another session of ECTR may be required. ECTR is recommended for patients with significant or potentially significant clinical poisoning. Intermittent HD is the preferred modality for ECTR in CBZ poisoning. Intermittent HP and continuous renal replacement modalities are alternatives if intermittent HD is not available.

HP: HP refers to anticoagulated blood that circulates through a cartridge containing adsorbent particles (AC particles or resin beads) onto which the poison can be adsorbed to achieve the goal of blood purification[87,88]. This modality is suitable for removing poisons with medium or large molecular weight, high lipid solubility, and high protein binding. CBZ is a highly lipid-soluble drug that can be rapidly distributed in tissues, and its plasma protein binding is as high as 70%-80%. Therefore, HP is historically identified as the preferred modality for extracorporeal removal in cases of severe CBZ poisoning[89-92], although the EXTRIP workgroup published a contrary opinion. Despite limitations such as early saturation of the cartridges, the successful removal of CBZ through either resin or charcoal HP has been reported with varying clearance efficiencies ranging from 25% to 55%[93-97]. In a recent study conducted by Yang *et al*[98], the authors concluded that the early initiation of HP during treatment of CBZ poisoning would significantly lower the serum concentration and minimize the CBZ detection time, leading to symptom relief and shortening of the overall treatment period. However, this procedure is often difficult to perform and carries risks such as thrombocytopenia, leukopenia, coagulopathy, and hypocalcemia, which are thought to be associated with cell adsorption and continuous replenishment of the AC[99,100]. Therefore, the frequent monitoring of platelet counts or application of new biocompatible polymer membranes is indispensable for decreasing these complications[101].

HD: HD takes advantage of the principle of diffusion, allowing poison to pass through a semipermeable membrane from a higher- to lower-level side to remove the poison in the blood. This modality is suitable for poisons with high water solubility, low molecular weight (< 500 D), medium molecular weight, and low protein binding. Although intermittent HP is historically preferred for the removal of CBZ, HD should be considered based on its theoretical superiority in clearing protein-bound poisons such as CBZ, and the EXTRIP workgroup recommends intermittent HD over HP. Indeed, several factors prove that HD is superior to HP. First, its clearance efficiency is superior. Although a previous study showed that HP has higher clearance than HD, the comparison was based on older, less efficient cuprophane dialyzers [5]. Recent data have shown that high-efficiency HD is almost as effective as charcoal HP and results in rapid clinical improvement[13,102-104] when equipped with a highly permeable high-flux membrane with increased dialysate flow, which produces comparable efficacy by allowing the removal of larger molecules and highly protein-bound poisons[105-109]. In addition, there is a risk of hemolysis. Blood flow circulating in cartridges during HP remains limited to 300-350 mL/min; however, the use of brand new catheters during HD enables blood flow up to 400 mL/min[110]. Furthermore, there are high amounts of free CBZ molecules and its metabolites in blood at increased concentrations, which are good candidates for removal by HD[111,112]. Second, the manipulability of HD is superior; HD is more available than HP, and HD is the preferred technique for dialysis for patients with acute kidney injury and end-stage kidney disease worldwide. Early initiation of ECTR is critical, considering that clinical improvements are likely associated with how quickly poisons can be cleared from the body. In addition, physicians and nurses are more familiar and experienced with HD; thus, this technique is more likely to be implemented with fewer delays and uncertainties. Third, outcomes of HD are superior; complications are less likely to occur with HD than with HP[113]. Finally, HD has a favorable cost compared with HP. A recent investigation of availability, time to initiation, and cost of ECTR in acute settings worldwide confirmed the lower cost of HD compared with other ECTRs (median cost ratio of HP:HD = 1.7)[114]. The high spending associated with HP is largely due to multiple replacements of expensive charcoal cartridges because of its easy saturation, which would decrease poison clearance[12,91]. Moreover, monitoring and treating complications of HP contribute to its high expenses.

Continuous renal replacement treatment: Continuous renal replacement treatment (CRRT), also known as continuous blood purification, is a treatment involving the continuous, slow removal of water and solutes. CRRT includes continuous venovenous HD, continuous venovenous hemodiafiltration (CVVHDF), and continuous venovenous hemofiltration[115]. These continuous therapies are usually performed in the ICU to facilitate management of hemodynamically unstable patients who cannot withstand high-efficiency intermittent treatments. Therefore, lower dialysate rates during CRRT (up

to 10 L/h) than the dialysate flow rates used in intermittent HD (500–800 mL/min) are routinely offered, leading to markedly lower clearance[5]. However, CRRTs play a better role in mitigating rebound effects than intermittent techniques, regardless of the drug clearance rate. Numerous studies are available documenting the use of CRRTs in patients with CBZ intoxication; however, techniques and outcomes vary substantially. Thus, the benefits of these techniques to eliminate CBZ from the body are unable to be determined[89,116-119]. Consequently, continuous techniques are regarded as low-priority modalities by the EXTRIP workgroup and are only advocated when intermittent treatments are unavailable (because of technical or personnel reasons in critical care settings). Nevertheless, some authors approve of the joint use of intermittent procedures and CRRTs in patients with poisoning to avoid "rebound phenomenon".

Recently, the addition of albumin to the dialysate appeared to improve CBZ clearance compared with conventional CRRT in some studies[120-124]. In a study conducted by Choi *et al*[122], the applied CVVHDF showed a 24% increase in CBZ clearance when using dialysate with the addition of 20% albumin. Another *in vitro* study using modeled continuous HD performed in 2009 also confirmed that CBZ clearance was significantly enhanced with 2.5% or 5% albumin-supplemented dialysate compared with control (albumin-free) dialysate[123]. This technique could be explained by basic principles of thermodynamic protein-binding affinity and solute movement along a concentration gradient. The albumin added to the dialysate works as a "sink" to bind CBZ that moves across the dialyzer membrane along the concentration gradient formed between the blood side and dialysate side[124]. However, extremely high costs have limited their widespread use. In addition, whether these procedures have superiority to either HP or HD remains unclear and further investigation is needed.

LRT

LRT is a relatively new method to improve the clinical manifestations of toxicity from overdose of certain drugs through administration of intravenous lipid emulsions (ILEs). ILE was conventionally used for parenteral nutrition and first applied in 1998 by Weinberg and colleagues[125] as a treatment option in toxicology. The first human case of ILE clinical use was reported by Rosenblatt *et al*[126] in 2006 to treat local anesthetic (bupivacaine) systemic toxicity. Since then, ILEs have been widely used in clinical toxicology as a life-saving treatment for local anesthetic-induced cardiotoxicity[127]. With further research, the field has expanded progressively with successful clinical translation and expansion of use to treat other types of non-local anesthetic lipophilic drug overdoses[128-132].

The ILE mechanisms of action are not entirely clear but can be partially explained by dynamic scavenging/partitioning and direct cardiovascular effects[133,134]. In 1998, Weinberg and colleagues originally proposed a mechanistic hypothesis, namely, that ILE provides a novel compartment into which lipophilic drugs circulating in the blood are able to partition, preventing them from affecting other organs. This theory was widely accepted and referred to as "the lipid sink". However, with improved understanding of this treatment, a "lipid shuttle" or a capture/release mechanism has been suggested in which ILEs play a role in accelerating the redistribution of drugs and moving drugs around, as opposed to acting like a "lipid sink" that catches and segregates drugs[135]. In addition, ILEs exert direct effects on myocardial tissue that improve cardiac output; however, the relevant potential mechanisms are not fully understood[136, 137]. Based on these mechanisms of action, ILEs have been used to manage toxicity from non-local anesthetic lipophilic drugs.

CBZ is a highly lipophilic molecule and can induce cardiotoxicity in cases of significant overdose. ILEs have been administered to treat CBZ intoxication in several cases with varying results[116,138-141]. ILE treatment was used in two case reports for CBZ-induced cardiotoxicity and showed beneficial effects[138,139]. In a retrospective study investigating the clinical effects of lipid emulsion for the treatment of childhood CBZ poisoning, researchers enrolled 48 patients and divided them into Group A (lipid emulsion + HP) and Group B (HP); a statistically significant difference was not observed in the blood concentration of CBZ between groups ($P > 0.05$). After 24, 48, and 72 h of treatment, the CBZ blood concentration in Group A was significantly lower than that in Group B ($P < 0.05$), and the researchers concluded that the lipid emulsion could be used for the treatment of CBZ poisoning in children to reduce the blood CBZ concentration as quickly as possible[142]. Although the sole effect of ILE in CBZ clearance has not been proven, ILE is still considered to be a potentially beneficial alternative to ECTR methods in CBZ intoxication. Whether and when to initiate LRT is discretionary and depends on the clinical judgment of the treating physician. Blood clotting and fat deposition commonly occur in extracorporeal circuits when combined with LRT[140,141], and thus should be monitored during therapy.

DISCUSSION

We conducted a retrospective review of selected literature. The case reports contained detailed data describing patient status and treatments, and an aggregate description was made (Table 1). After discussion and analyses of CBZ poisoning cases, we established recommendations for the treatment of CBZ poisoning (Table 2); 67 patients were included and no randomized controlled trials were identified. The median CBZ peak concentration was 39.0 mg/L and the median age was 42.3 years. Notably, all patients had varying degrees of consciousness impairment, which were due to individual differences. In addition, some patients experienced respiratory depression, dysrhythmias, hypotension, seizures, or a combination of these symptoms. Among the patients, 32 showed varying degrees of respiratory depression. Overall, 4 cases were described as deaths caused by CBZ poisoning rather than the effect of the treatment[43,44,105]. GL is a simple and convenient treatment, but only 6 patients received GL because the treatment is prohibited in patients with impaired consciousness, recent surgery, no airway protection, risk of GI bleeding and perforation, or potential for increased risk

Table 1 Clinical outcomes of the 67 patients described in the case reports

Patient demographics	Values
Median age (yr)	25 (1.5-85)
Male sex	49.3
Poisoning exposure	
Mean peak carbamazepine concentration in mg/L	39.0 (17.7-93.8)
Clinical symptoms and signs	
Respiratory depression	47.8
Decreased consciousness	100
Seizure	20.9
Hypotension	14.9
Dysrhythmias	19.4
Treatment measure[1]	
Supportive care	9.0
Gastric lavage	29.9
Multiple-dose activated charcoal	58.2
Hemoperfusion	22.4
Hemodialysis	22.4
Continuous renal replacement treatment	12.0
Plasma exchange and plasmapheresis	4.5
Lipid resuscitation therapy	4.5
Outcome	
Recovery	82.0
Sequelae	12.0
Fatalities	6.0

[1]Some patients received more than one treatment.
Data are presented as *n* (range) or %. The source of cases is listed in Supplement Material.

and severity of aspiration[16,19,21,23,26,28]. In these situations, considering the patient's economic conditions and affordability, MDAC was chosen instead of GL. For decades, MDAC has been used as a universal antidote for the majority of poisons because of its ability to prevent absorption of the most toxic agents from the GI tract and enhance the elimination of some agents already absorbed[143,144]. The optimum dose of MDAC is difficult to precisely determine for an individual patient. Optimum dosage depends on many variables such as the volume and pH of gastric and intestinal fluid, and the presence of other agents or food absorbed by AC[145-148]. Notably, repeated administration is still effective against substances that stay longer in the stomach, which is another advantage of MDAC. The recommended dose for adults is typically 50 g; however, the amount administered to children is determined based on body weight (0.5-1 g/kg). Reported complications and adverse effects of MDAC include diarrhea, constipation, vomiting, pulmonary aspiration, and intestinal obstruction. Consequently, MDAC should be used with caution in the following situations: unprotected airway; presence of intestinal obstruction; or GI tract not anatomically intact. Therefore, intestinal motility in patients receiving MDAC should be continuously monitored as necessary to maintain electrolyte and water balance.

HP was the most common treatment for the patients in our review, accounting for 58.2% of cases. HP was considered the most timely and effective treatment for patients with excessive CBZ toxicity and life-threatening symptoms because it can remove mid-to-large-sized toxin molecules bound to proteins. However, the earlier enthusiasm for HP has decreased and HD is currently the treatment of choice for poisoned patients. HP presents some challenges compared with HD. For example, HP is associated with more complications than HD (namely, hypocalcemia, leucopenia, thrombocytopenia[147,148]), and the rate of complications is greater during HP than HD. Furthermore, HP is more expensive and results in the early saturation of columns. Notably, the same percentage of patients received HD and CRRT therapy (22.4%). HD and CRRT are commonly used to provide renal support to critically ill patients with acute kidney injury, particularly those who are hemodynamically unstable. Although initially developed as an arteriovenous therapy, most CRRT is now performed using pump-driven venovenous extracorporeal circuits. However, initiation of CRRT requires vascular access, which is generally established through placement of a large-bore double lumen catheter in an internal jugular, femoral, or

Table 2 Executive summary of recommendations for the treatment of carbamazepine poisoning

General statement
The primary treatment for CBZ poisoning is GL
A mainstay of treatment is multiple-dose activated charcoal
ECTR is suggested in cases of severe CBZ poisoning
Intermittent hemodialysis is the preferred ECTR for CBZ poisoning
Lipid resuscitation therapy is an effective adjunctive treatment to ECTR
Supportive care
Severe central nervous system depression requires endotracheal intubation
To avoid masking subsequent seizures, short-acting neuromuscular blockers are recommended
Isotonic crystalloid to correct hypotension should be considered first; when isotonic crystals do not work, direct-acting vasopressors can be applied
QRS prolongation is treated with sodium bicarbonate
Management precautions
GL is contraindicated when patients have impaired consciousness, recent surgery, no protection of airway, risk of gastrointestinal bleeding and perforation, and the potential for increased risk and severity of aspiration
Multiple-dose activated charcoal should be used with caution in cases of an unprotected airway, presence of intestinal obstruction, or gastrointestinal tract not anatomically intact

CBZ: Carbamazepine; ECTR: Extracorporeal treatment; GL: Gastric lavage.

subclavian vein. Furthermore, hypotension during CRRT is common, occurring in some series in more than one-third of patients, but is most often unrelated to the CRRT procedure. Increased hemodynamic instability due to ultrafiltration may be the most likely treatment-related factor contributing to hypotension[149]. Therefore, we conclude that in the absence of accurate, scientific data indicating effectiveness and risk, a sound recommendation for the use of CRRT cannot be made. Again, the treating physician must weigh the theoretic benefit against the potential for complications in each clinical scenario. HD is indicated for the therapeutic management of acute poisoning or drug overdose and is the most commonly favored extracorporeal technique in poisoning situations due to its availability, cost, and safety profile. With the development of science and technology, the advent of high-efficiency, high-flux dialyzers has rendered other techniques, such as HP, almost obsolete. Furthermore, HD enables the correction of acid-base and electrolyte abnormalities.

Among patients, plasma exchange and plasmapheresis as well as lipid emulsion were the least frequent (both 4.5%). Plasma exchange and plasmapheresis refer to the extracorporeal technique preformed in an apheresis device where the patient's plasma is separated from whole blood and removed, and the cellular blood components are returned to the patient together with a replacement fluid[150]. Therapeutic procedures commonly include therapeutic plasma exchange and red blood cell exchange with or without depletion, in addition to more specialized procedures, such as low-density lipoprotein (LDL) apheresis and extracorporeal photopheresis, which was widely used in China to treat patients with coronavirus disease 2019[151]. However, because performing extracorporeal photopheresis is complex and requires precision, the method is rarely used in drug intoxication cases. The mechanism of action in LDL apheresis creates an expanded, intravascular lipid phase in which equilibria are established that drive the offending drug from target tissues into the newly formed "lipid sink". Based on this theory, LDL has been considered a candidate for generic reversal of toxicity caused by overdose of any lipophilic drug. However, the use of LDL apheresis requires caution, especially in patients with a history of hypersensitivity to lipid emulsion or ingredients (*e.g.*, eggs, soy), severe sepsis, severe liver disease, acute pancreatitis, and acute myocardial infarction. Therefore, we suggest that LDL apheresis be considered under circumstances of refractory hemodynamic instability.

CONCLUSION

Herein, we presented recommendations for therapies in CBZ poisoning. Risk assessment of selected case reports showed that in most poisoned patients, general supportive measures usually suffice, including airway management and protection, ventilatory support, fluid resuscitation, correction of electrolyte and acid-base disorders, and management of poison-related hypo/hyperthermia. Primary GI decontamination with AC and routine GL are widely used. Aggressive ECTR is required for rapid and substantial removal of CBZ and its metabolites when clinical symptoms and signs are serious or deteriorated. Choice of ECTR modality should be based on clearance efficiency, availability, cost, and complications. Among the various ECTRs available, HD provides the best expected removal for CBZ poisoning with the lowest incidence of complications and should therefore be the preferred modality in most cases.

FOOTNOTES

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Abstract

The latest global cancer burden data released by the International Agency for Research on Cancer of the World Health Organization in 2020 shows that there were 19.29 million new cancer cases worldwide, with 4.57 million in China, ranking first. The number of cancer survivors is increasing, with a 5-year survival rate exceeding 85%, but there are emotional disorders. Cognitive behavioral therapy (CBT) can improve negative emotions and has significant effects on patients. However, there is a limited number of physicians and high costs, so internet interventions have become a solution. The feasibility of web-based interventions for breast cancer patients has been proven. Research on internet-delivered CBT is also increasing. The purpose of this study was to review the concept of web-based CBT and its application status in cancer survivors, in order to provide relevant intervention for scholars and provide reference and supplement for patients to provide psychological therapy.

Key Words: Cancer survivors; Network; Cognitive behavioral therapy; Negative emotions

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Core Tip: The number of cancer survivors is increasing, but emotional disorders persist. Cognitive behavioral therapy (CBT) has shown significant effects in improving negative emotions. Due to limited physicians and high costs, internet interventions have become a solution. Web-based interventions for breast cancer patients have proven feasible, and research on internet-delivered CBT is growing. It is helpful to reviewing web-based CBT and its application in cancer survivors and provide intervention insights for scholars and psychological therapy references for patients.

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INTRODUCTION

According to the latest global cancer burden data released by the International Agency for Research on Cancer[1] of the World Health Organization, there were 19.29 million new cancer cases worldwide in 2020, and 4.57 million in China, which ranks first in the world. Thanks to improvements in diagnosis and treatment, the number of cancer survivors is increasing, with 5-year survival rates > 85%. Cancer survivors have varying degrees of mood disorders, including negative emotions, cancer-related fatigue, and sleep disturbances. It has been reported that mood disorders in cancer survivors are 2-4 times more prevalent than in the general population, leading to a lower quality of life, poorer daily functioning, and poor prognosis[2,3]. Meta-analyses show that cognitive behavioral therapy (CBT) improves negative mood, with effect sizes of 0.97 and 0.95 for patients with mood disorders, and 0.39 and 0.44 for cancer patients and survivors. However, due to the limited number of trained therapists, high cost, and limited time and space for cancer patients and survivors, providing CBT to patients in need remains a challenge[4]. Interventions delivered *via* the internet have become an increasingly popular way to overcome these challenges, and a review of e-health intervention systems for breast cancer patients and survivors demonstrated the universal feasibility and acceptability of interventions delivered *via* the internet[5]. There are also increasing studies on the intervention of patients with internet-delivered CBT (ICBT)[6-8].

OVERVIEW OF CBT

The origins of CBT can be traced back to Skinner and Joseph[9], who pioneered the CBT movement in the 1950s. CBT refers to changing adverse emotional reactions by correcting irrational cognitive concepts and/or behaviors, so as to resolve a series of physiological and psychological problems in patients[10]. In other words, changing behaviors will lead to emotional and cognitive changes. ICBT provides health education information to patients through the internet[11]. In ICBT, patients can obtain the same health information as CBT (such as psychological education on cognitive behavioral patterns, cognitive reorganization, behavioral skills, and relapse prevention)[12-14]. The material content of ICBT usually includes text, image, video and audio, *etc*., and generally the intervention duration varies from 5 to 15 wk[15]. CBT is a problem-centered and action-oriented approach that aims to eliminate negative emotions and behaviors by changing thoughts and behaviors to change negative cognition[9]. It focuses more on the current situation than on past experiences, mental problems, and connections between wrong ways of thinking and ways of acting, which helps patients to better identify their own negative thinking, use cognitive technology to combat negative thinking, correct wrong cognition to improve anxiety, depression and other negative emotions, and relieve pain, sleep disorders, and other physical and mental symptoms. This study conducted a literature search using the keywords "internet-delivered cognitive-behavioral therapy" or "web-based cognitive-behavioral therapy" and "tumor" or "cancer" on PubMed, China National Knowledge Infrastructure, and Wanfang Database to retrieve relevant Chinese and English articles. After screening, a total of 49 articles were obtained for reviewing the concept of ICBT and its application in cancer survivors.

APPLICATION AND EFFECT OF CBT IN CANCER SURVIVORS

Reducing negative emotions

Compared with healthy people, cancer patients are more likely to experience negative emotions such as anxiety and depression[16]. A large Canadian study on mental disorders in 10153 cancer patients[17] showed that 19% had clinical anxiety symptoms, 22.6% had subclinical anxiety symptoms, 12.9% reported clinical depression symptoms, and 16.5% reported subclinical depression symptoms. Therefore, it is important to find treatment that can improve the psychological problems of cancer patients to improve their prognosis. Palay *et al*[17] found that breast and prostate are common cancer types with high survival rate, and such cancer survivors have some psychological distress, so they developed ICBT to improve the anxiety and depression symptoms of cancer patients in their daily life. The study began with screening of cancer patients at cancer hospitals and controlled follow-up of patients after initial treatment for symptoms of anxiety and depression in their daily lives. A total of 206 cancer patients were recruited for the study. These participants were randomly assigned to either the intervention group or the waiting control group for 10 wk each, with follow-up at week 5 (T2/mid-intervention), week 10 (T3/post-treatment), and week 34 (T4/6 mo post-treatment). The ICBT intervention program for improving anxiety and depression symptoms in cancer patients was developed by clinical psychologists who modified the original face-to-face CBT manual[19,20]. It lasted for 1 wk and consisted of eight modules, each consisting of written materials and audio exercises, writing tasks, examples of cancer patients, and expert videos. Participants completed a weekly training diary and mailed it to a therapist, who gave corresponding asynchronous written feedback[21]. The basic points of this treatment plan are as follows: (1) Nine therapists: Eight CBT-trained masters in psychology and

one experienced psychologist; (2) Supervision: Based on written feedback from therapists to participants, a manual reminder guide was developed, undertaken by therapist assistants, to urge participants to complete online questionnaires at stages T2, T3 and T4. If participants do not complete the questionnaire within 1 wk, they will receive three reminder emails, and if they do not respond, a research assistant will call to ask the reason; (3) Treatment compliance: To improve compliance of participants, researchers will give gifts or bonuses to participants at the middle and end of treatment as incentives; and (4) Internet platform: This is a website compatible with smart phones, and patients carry out daily exercises through their personal accounts. The waiting control group was given a cancer hospital health manual and followed up with a questionnaire at four time points. The study used the State-trait Anxiety Scale, the Patient Health Depression Questionnaire and the World Health Organization Quality of Life Index questionnaire[22-24] (Figure 1).

This study found that 5 wk after intervention, anxiety and depression in the ICBT group were significantly lower than those in the waiting control group[25], indicating that anxiety and depression were improved immediately after intervention. Model fitting analysis showed that depression scores were in line with a log-linear curve, indicating that the improvement in the ICBT group occurred at the beginning of the study and continued to improve over a period of time. At the 6-mo follow-up assessment, the improvement in anxiety and depression was 2.35 times greater in the ICBT group than in the waiting control group, and was effective in maintaining its effect on patients' negative mood. A meta-analysis showed that mindfulness-based behavioral therapy can be used as a basic treatment for emotional rehabilitation of cancer [26], while interventions provided by the internet may alleviate the suffering of cancer survivors who are unable to access face-to-face psychotherapy[27] (Figure 1).

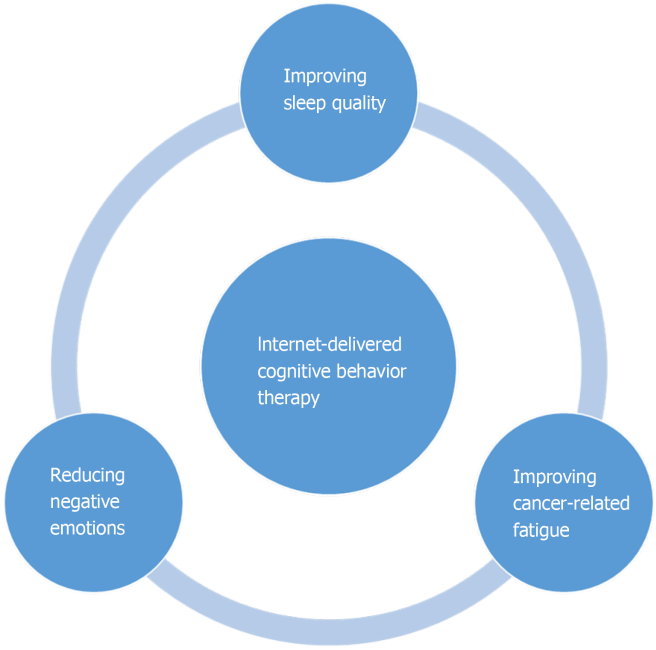
Improving sleep quality

Sleep deprivation can have significant effects on daily functioning, mood, and self-management in cancer survivors. Sheikhzadeh *et al*[28] developed ICBT for breast cancer patients with insomnia by combining mindfulness meditation and CBT for insomnia. The study used two parallel randomized controlled trials in which 50 patients with cancer insomnia were recruited from 10 hospitals and randomly assigned 1:1 to a mindfulness intervention group or an education-only control group. The mindfulness intervention included a 6-wk online self-directed learning module that covered mindfulness meditation, sleep challenges, and behavioral strategies for improving sleep. The intervention strategy focused on using mindfulness as a sleep self-management technique to increase total sleep time and sleep efficiency. The development of the intervention module was published online. Each module each week contains instructional content on sleep and mindful meditation, using interactive text, video and audio meditation. Each module lasts about 20 min and can be completed at a time of the participant's choosing. There is also a message board for interaction with other participants and researchers[29]. During the day, patients communicate with researchers *via* text or email to obtain support. Reminders to complete daily sleep diaries and weekly modules were sent to participants at intervals by text message or email. During the study, participants completed an online or paper sleep diary each morning, which was modified to include symptoms of sleep disturbances and reports of daily meditation practices. At the end of the second week of the program, weekly feedback reports on adherence to the participants' personally recommended sleep schedules were provided *via* email. The control group was given only health education and no mindfulness or meditation (Figure 1).

The study found that ICBT significantly improved insomnia symptoms. After 6 wk of intervention, 71.2% of patients in the intervention group had sustained significant improvement in insomnia and fatigue symptoms. This study innovatively addressed sleep problems in cancer survivors, using a self-managed study design and methodology that was both available and cost-effective for a large number of cancer survivors, and larger randomized controlled trials can be conducted in the future to guide and refine intervention regimens (Figure 1).

Improving cancer-related fatigue

Fatigue is a symptom commonly experienced by cancer survivors at all stages of disease development. Survivors identified fatigue as an important problem that was not adequately addressed by healthcare providers[30]. Fatigue has a greater negative impact on functioning and health-related quality of life than other symptoms such as pain or depression [31-33]. Mak *et al*[34] selected 100 cancer patients with severe fatigue symptoms from 160 patients diagnosed with cancer according to inclusion and exclusion criteria for an 8-wk randomized controlled trial. The project was developed based on MacDonald and O'Hara's 10 elements of mental health[35], with resources for mental health promotion from the World Health Organization and government reports from the United Kingdom and Australia[36,37]. ICBT courses include didactic reading (such as transmitting Buddhist views on the nature of human suffering), experiential learning (such as guided meditation), and everyday life applications (such as developing an awareness of how attachment to letting go of a person can lead to inner peace). In order to improve the user experience, the project improved on the basis of the preliminary design. Weekly health tracking, built-in multimedia in each class, and dynamic content display made the content more interactive. The page and content color coordination, theme consistent graphics, and easy navigation made the web page more aesthetically attractive. The project incorporated the core concepts of traditional Buddhism, including discernment, compassion, impermanence, interdependence and nonattachment. By incorporating our mindfulness training into a traditional Buddhist foundation, the training program was designed to help participants build their own foundation of practice. Such an intention will lay the foundation for continuous and regular practice and may potentially influence the outcome of practice[38,39]. Participants were also given videos of stretching exercises, body scans, and audio of sitting meditation to guide them through the exercises. During the intervention, participants were given worksheets that included a mood diary, cognitive reconstruction, and a healthy lifestyle program to record their responses. All content was developed by members of the research team, who were clinical psychologists and mindfulness practitioners. The control group received routine nursing (Figure 1).



DOI: 10.5498/wjp.v13.i11.831 **Copyright** ©The Author(s) 2023.

Figure 1 Application and effect of internet-delivered cognitive behavioral therapy in cancer survivors.

The study used the Cancer Related Fatigue Scale and the European Organization for Cancer Research and Treatment Quality of Life Scale to assess patients' quality of life and fatigue symptoms. The results showed that ICBT could significantly reduce cancer-induced fatigue and improve the quality of life of patients. The web page was designed reasonably, and course of treatment was moderate, with good patient feedback and high treatment compliance. Compared with face-to-face interventions, internet-based interventions are more accessible and affordable, and have the potential to satisfy the need to promote and prevent mental health in community settings and are worth scaling up in the future (Figure 1).

Limitation of ICBT

High dropout rate and poor compliance. Since ICBT courses are carried out in a standardized content and structured format, and therapists are not able to provide timely feedback and adjust the program according to the patient's response, this affects patient compliance[40]. Many complex problems in practice. Implementation of ICBT in five different European countries faced issues such as how to integrate it into the mental health care system, how to recruit patients, how to ensure the quality of the work of therapists, and how to provide long-term sustainable ICBT treatment[41]. Many influencing factors are unclear. At present, there are few studies on factors affecting treatment outcomes. One study explored the influ-encing factors from the content of emails from patients and therapists, and found that affirmation, encouragement, and self-exposure by therapists had a positive impact on treatment outcomes[42].

CONCLUSION

CBT is commonly used as first-line treatment for cancer survivors[43], and the American Medical Association recommends[10] that CBT be administered personally by trained therapists to promote self-management in cancer patients. Face-to-face CBT has been proven to be effective and worthy of promotion, but due to time, space and economic constraints, not all patients can easily access this treatment. With the increasing popularity of the internet, the combination of the internet and continuous care, and the full use of the advantages of the internet, can achieve the goal of promoting health education and prevention. ICBT has the advantages of low cost, easy access, and not being limited by time and space. ICBT can promote cancer patients' self-management, improve negative emotions, improve sleep quality, and relieve cancer-induced fatigue[44-46].

The research of the application of ICBT in cancer patients were summarized in Table 1. In the future, researchers can explore the influence of the duration of ICBT intervention on the intervention effect, so as to select the appropriate intervention time. It is imperative to cultivate high-quality therapists with a background in psychological medicine. In addition, ICBT is a psychological intervention that requires high-quality, multicenter, and large-sample randomized controlled trials. Qualitative interviews and descriptive data collection can be carried out to understand patients' subjective feelings, and improve intervention methods and guide intervention research.

Table 1 Research of the internet-delivered cognitive behavioral therapy application in cancer patients

Ref.	Patients (*n*)	Intervention	Indicators	Conclusion
Nissen *et al* [18]	Cancer survivors (1282)	Therapist-assisted iMBCT	Outcomes of anxiety and depression	iMBCT is a helpful intervention for cancer survivors suffering from symptoms of anxiety
Zachariae *et al*[47]	Breast cancer survivors (255)	ICBT-i or waitlist control	Sleep-related outcomes	ICBT-i appears to be effective in breast cancer survivors, with additional benefit in terms of reduced fatigue
Nissen *et al* [48]	Breast- and prostate cancer survivors (82)	iMBCT	Improvement in anxiety and depression scores from baseline to post-treatment and from baseline to six-months follow-up	iMBCT can be provided for cancer survivors regardless of their age, educational level, and time since diagnosis (up to five years) and therapeutic alliance is not crucial for treatment response
Dirkse *et al* [49]	Cancer survivors with symptoms of anxiety or depression (86)	ICBT program guided by a technician	Anxiety, depression, fear of cancer recurrence, quality of life	ICBT was associated with improved levels of anxiety, depression, fear of cancer recurrence, and quality of life
Murphy *et al*[50]	Breast cancer patients with generalized anxiety disorder (14)	ICBT	Health status, adherence, acceptability	ICBT has significant potential to be a suitable modality supervised by clinican
Murphy *et al*[51]	Cancer survivors (114)	ICBT or TAU	Anxiety and depression symptoms, fear of cancer recurrence, quality of life	Clinician-supervised iCBT has significant benefits for cancer survivors with clinical depression and anxiety disorders
Carbajal-López *et al*[52]	Gastrointestinal stromal tumors (99)	ICBT or internet-delivered cognitive program	General fatigue, reduced motivation, distress and global health status	Both intervention programs showed reductions in the dimensions of fatigue and improvements in distress and dimensions of quality of life

iMBCT: Internet-delivered mindfulness-based cognitive therapy; TAU: Treat-as-usual; ICBT: Internet-delivered cognitive behavioral therapy.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Effects of combined spinal-epidural anesthesia on anxiety, labor analgesia and motor blocks in women during natural delivery

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Abstract

BACKGROUND

The background of this study was analgesia in natural delivery. The combined spinal-epidural anesthesia has obvious analgesic effect on the parturients in natural labor, and combined spinal-epidural anesthesia has been widely used in anesthesia for various diseases.

AIM

To study the effects of combined spinal-epidural anesthesia on anxiety, labor analgesia, and motor blocks in parturients during natural delivery.

METHODS

A total of 120 women who gave birth at Changning District Maternal and Child Health Hospital between December 2021 to December 2022 were included; a random number table approach was employed to divide the women into a control group and a joint group, with each group consisting of 60 women. The control group was given epidural anesthesia, while the joint group was given combined spinal-epidural anesthesia. The visual analog scale (VAS) was used to evaluate the degree of maternal pain. Comparisons were made between the two groups' conditions of childbirth and the duration of labor. Apgar scores were used to evaluate the status of the newborns at birth; Self-rating Anxiety Scale (SAS) and General Self-Efficacy Scale (GSES) scores, umbilical artery blood gas analysis indices and stress indices were compared between the two groups; and the frequencies of motor block and postpartum complications were analyzed.

RESULTS

In comparison to the control group, in the joint group, the VAS scores for the first, second, and third stages of labor were lower ($P < 0.05$). The rates of conversion to cesarean section and postpartum blood loss in the joint group were lower than those in the control group ($P < 0.05$). No significant differences were observed in the Apgar score, the duration of the first stage of labor, or the total duration of

labor between the two groups ($P > 0.05$). The second and third stages of labor in the joint group were shorter than those in the control group ($P < 0.05$). When compared to the control group, the postpartum SAS score of the joint group was lower, while the GSES score was greater ($P < 0.05$). Between the control group and the joint group, the differences observed in pH, arterial carbon dioxide partial pressure, arterial oxygen partial pressure, or arterial hydrogen ion concentration were not significant ($P > 0.05$). Nitric oxide, cortisol, and adrenaline levels were lower in the joint group than in the control group ($P < 0.05$). There were no substantial differences in Bromage grade or rate of complications between the two groups ($P > 0.05$).

CONCLUSION

For parturients during natural delivery, combined spinal-epidural anesthesia can reduce anxiety, provide labor analgesia, shorten labor time, and reduce postoperative stress levels but did not result in a motor block.

Key Words: Combined spinal-epidural anesthesia; Natural delivery; Anxiety level; Labor analgesia; Motor block

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Core Tip: The pain of parturients in natural delivery is serious. Spinal anesthesia and epidural analgesia are widely used, but the analgesia effect is not good, and the nerve block effect of lumbar epidural anesthesia is better. The objective of this study was to compare the effects of combined epidural and lumbar anesthesia on labor analgesia and movement block.

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INTRODUCTION

Labor is a complicated physiological and psychological process, and labor pain is a subjective feeling of the human body that lacks objective indicators. Currently, combined spinal-epidural anesthesia is widely used to relieve the pain of parturients during natural childbirth, which has less impact on contraction pain than other analgesic methods[1]. However, various research studies have shown that epidural anesthesia alone has a poor analgesic effect in parturients. Based on this fact, intraspinal anesthesia can be used to effectively enhance the analgesic effect[2]. Combined spinal-epidural anesthesia has a more rapid analgesic effect and better nerve block efficacy than epidural anesthesia[3]. Childbirth is a natural biological process as well as a complex period involving volatile emotions. Related research suggests that the intensity of labor pain is associated with individual pain thresholds as well as many other influencing factors[4]. Poor mood around the time of delivery can directly reduce a woman's pain threshold, making her more sensitive to pain. In addition, severe pain during childbirth increases the fear, tension, and anxiety of parturients, forming a vicious cycle, which keeps them in a state of high stress and has adverse effects on delivery[5,6]. Therefore, reducing negative emotions in patients during childbirth is crucial for smooth deliveries. Based on the above, this study explored the effects of combined spinal-epidural anesthesia on anxiety levels, labor analgesia and motor blocks in women during natural delivery, with the view of selecting a better method of labor anesthesia and promoting smooth deliveries.

MATERIALS AND METHODS

Clinical data

A total of 120 women who gave birth in Changning District Maternal and Child Health Hospital from December 2021 to December 2022 without signs of cesarean section were studied. By employing a random number table, they were separated into control and joint groups, each of which included 60 women. Table 1 demonstrates that no significant differences were present in the general data between the two groups ($P > 0.05$).

The inclusion criteria were as follows: (1) Women aged 23-34 years old; (2) Women with American Society of Anesthesiologists physical status grade I; (3) Primiparas; and (4) Women with a gestational age of 36-40 wk. The exclusion criteria were as follows: (1) Patients with a medical history of hematological diseases; (2) Patients with long-term use of anticoagulants or drugs that affect coagulation function; (3) Patients with contraindications for combined spinal-epidural anesthesia; and (4) Patients with pregnancy-induced hypertension and other obstetric complications.

Methods

The joint group was given combined spinal-epidural anesthesia. When the uterine orifice was opened to 1 cm, puncture was performed in the lumbar L2-3 space. After successful subarachnoid puncture, cerebrospinal fluid flow was

Table 1 Comparison of general data between the two groups

Classification	Joint group (*n* = 60)	Control group (*n* = 60)	*T* value	*P* value
Age (yr)	26.79 ± 3.18	27.03 ± 3.21	0.411	0.682
Gestational age (wk)	39.35 ± 0.24	39.28 ± 0.21	1.700	0.092
Number of pregnancies	1.84 ± 0.17	1.89 ± 0.21	1.433	0.154
Parity	1.59 ± 0.12	1.61 ± 0.15	0.806	0.422
Estimated newborn body mass (kg)	3.58 ± 0.53	3.65 ± 0.49	0.751	0.454

continuous. A subarachnoid injection of 1 μg sufentanil (Yichang Humanwell Pharmaceutical Co., LTD., batch number: SFDA approval number H20054171) and 0.2 mg ropivacaine (Jiangsu Hengri Pharmaceutical Co., LTD., batch number: SFDA approval number H20060137) was given. Epidural catheterization was performed. After successful catheterization, 3 mL of 1.5% lidocaine (Shanghai Pujin Linzhou Pharmaceutical Co., LTD., batch number: SFDA approval number H41022244) was given as the experimental dose. After confirming correct placement in the epidural space, the epidural catheter was fixed with adhesive tape. Sufentanil (0.5 μg/mL) and +0.1% ropivacaine was combined with an epidural infusion pump. The first dose of the infusion pump was set at 10 mL, the patient-controlled analgesia dose was set at 9 mL, and the patient-controlled lockout time was 20 min. The infusion pump was turned on 1 h after anesthesia. Epidural anesthesia was given to the control group with the same specific method as that in the joint group.

The observation targets were as follows: (1) Labor pain: The degree of labor pain in each stage of labor was evaluated by employing the visual analog scale (VAS)[7]. The scores ranged from 0-10, and the severity of the pain increased with the score; (2) Childbirth-related conditions: The two groups' rates of conversion to cesarean section, forceps-assisted delivery, and postpartum blood loss and newborn Apgar scores were compared. The Apgar score was utilized to evaluate the status of newborns[8]. The Apgar scores ranged from 0-10, with a score of 10 representing healthy newborns and a score < 7 indicating asphyxia; (3) Labor duration: Between the two groups, the first, second, and third stages of labor as well as the overall duration of labor were compared; (4) Emotion: The Self-Rating Anxiety Scale (SAS) was employed to evaluate the anxiety levels of patients[9]. The scores ranged from 20-80, and a score of > 50 indicated anxiety. The General Self-Efficacy Scale (GSES) was utilized to evaluate the patients' self-efficacy[10], with scores ranging between 10 and 40 points. Higher scores suggested a stronger sense of self-efficacy; (5) Blood gas analysis indices of the umbilical artery: After delivery, 1 mL of umbilical artery blood was extracted with a heparin anticoagulant syringe. Then, the pH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2) and arterial hydrogen ion concentration (BE) of the maternal umbilical artery were detected by an ABL77 automatic blood gas analyzer (Radiometer, Denmark); (6) Stress index: Before and 3 d after delivery, 3 mL of maternal venous blood was drawn and subjected to centrifugation, serum cortisol (Cor) and adrenaline (ADR) levels were measured by ELISA, and serum nitric oxide (NO) levels were measured by the NO enzyme method; (7) Degree of motor block: The modified Bromage score was employed to evaluate the degree of motor block[11]. Level 0 indicated that there was no motor block, and the lower limbs could be raised; level 1 indicated the inability to lift the thigh; level 2 indicated difficulty in bending the knee; and level 3 indicated difficulty in bending the ankle; and (8) Complications: In both groups, the frequency of postoperative issues such as hypotension, nausea, and vomiting was measured.

Statistical analysis

SPSS 22.0 software was utilized to process the data. Counting data are reported as percentages, and differences between groups were compared by Fisher's exact test or the χ^2 test. Measurement data are reported as mean ± SD after the normality test, and the differences between groups were compared *via t* tests. Ranked data were analyzed by *Z* tests. $P < 0.05$ indicated a statistically significant difference.

RESULTS

Comparison of labor pain between the two groups: Before anesthesia, no significant difference was observed in the VAS scores of the two groups ($P > 0.05$). In comparison to the control group, in the joint group, the VAS scores for the first, second, and third stages of labor were lower ($P < 0.05$) (Figure 1).

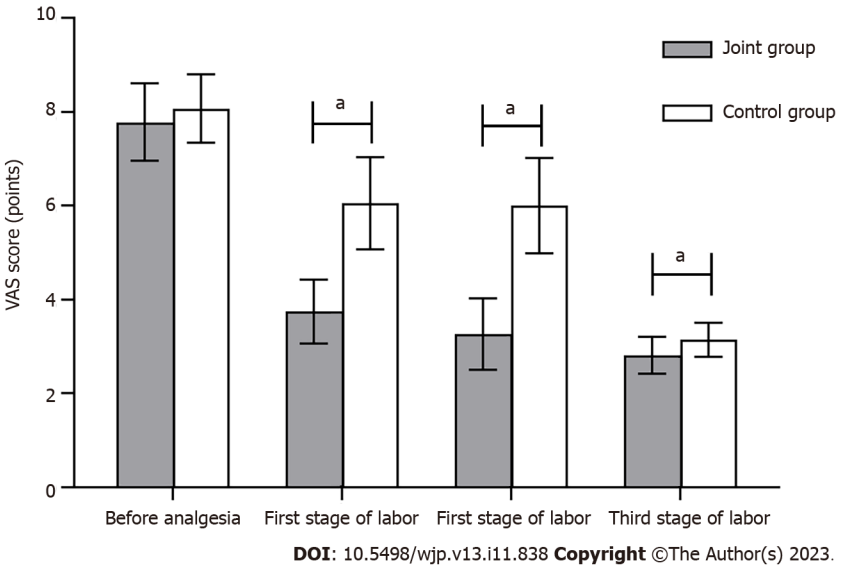
Comparing the childbirth-related conditions between the groups: The rates of conversion to cesarean section and postpartum blood loss were lower in the joint group than in the control group ($P < 0.05$); no significant differences were observed in the two groups' Apgar scores ($P > 0.05$) (Table 2, Figure 2).

Comparison of labor duration between the two groups: The initial stage of labor and the overall duration of labor did not substantially differ between the two groups ($P > 0.05$); the joint group experienced slightly shorter second and third stages of labor in comparison to the control group ($P < 0.05$), as shown in Figure 3.

Comparison of anxiety and depression between the two groups: Prenatal SAS and GSES scores did not differ significantly between the groups ($P > 0.05$). The SAS scores of both groups were lower in the postpartum period than the prenatal period, and the SAS scores of the joint group were lower than those of the control group ($P < 0.05$). The GSES scores were higher in both groups in the postnatal period compared to the corresponding scores in the prenatal period,

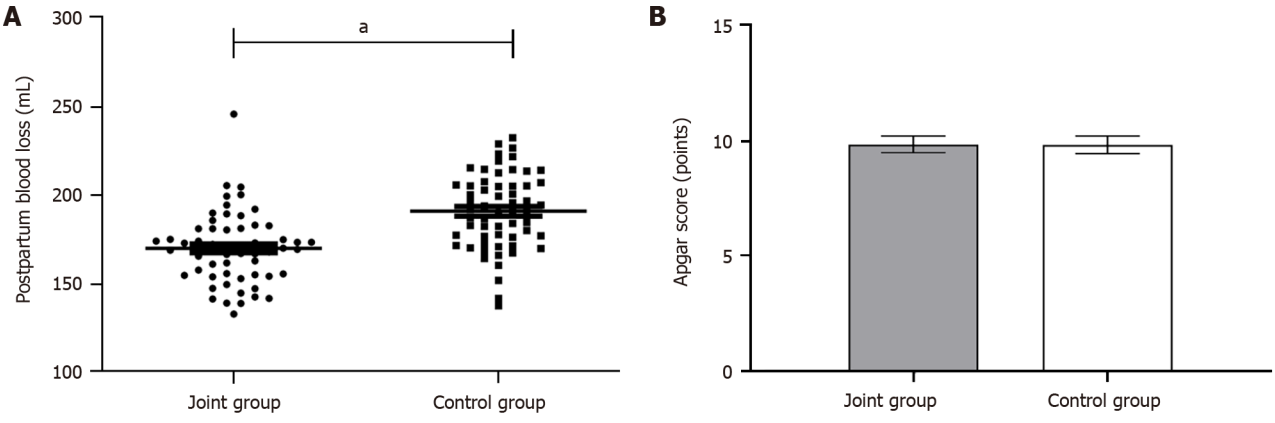
Table 2 Comparison of childbirth-related conditions between the two groups

Group	*n*	Rate of conversion to cesarean section	Rate of forceps-assisted delivery
Joint group	60	0.00 (0)	3.33 (2)
Control group	60	8.33 (5)	6.67 (4)
P value		< 0.05	> 0.05



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Figure 1 Comparison of visual analog scale scores between the two groups (scores). [a]*P* < 0.05, comparison with the joint group in the same period. VAS: Visual analog scale.



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Figure 2 Comparison of childbirth-related conditions between the two groups. A: Comparison of postpartum blood loss between the two groups; B: Comparison of apgar score between the two groups. [a]*P* < 0.05, comparison with the joint group.

with the joint group having higher scores than the control group ($P < 0.05$) (Figure 4).

Comparison of blood gas analysis indices of the umbilical artery between the two groups: The changes observed in pH, PCO_2, PO_2, and BE between the control and joint groups were not significantly different ($P > 0.05$), as shown in Figure 5.

Comparison of stress indices between the two groups: No significant differences were observed in the prenatal Cor, ADR, and NO levels between the groups ($P > 0.05$). Following delivery, the levels of Cor, ADR, and NO increased in both groups compared to those before delivery. Additionally, the scores in the control group were elevated compared to those in the joint group ($P < 0.05$) (Figure 6).

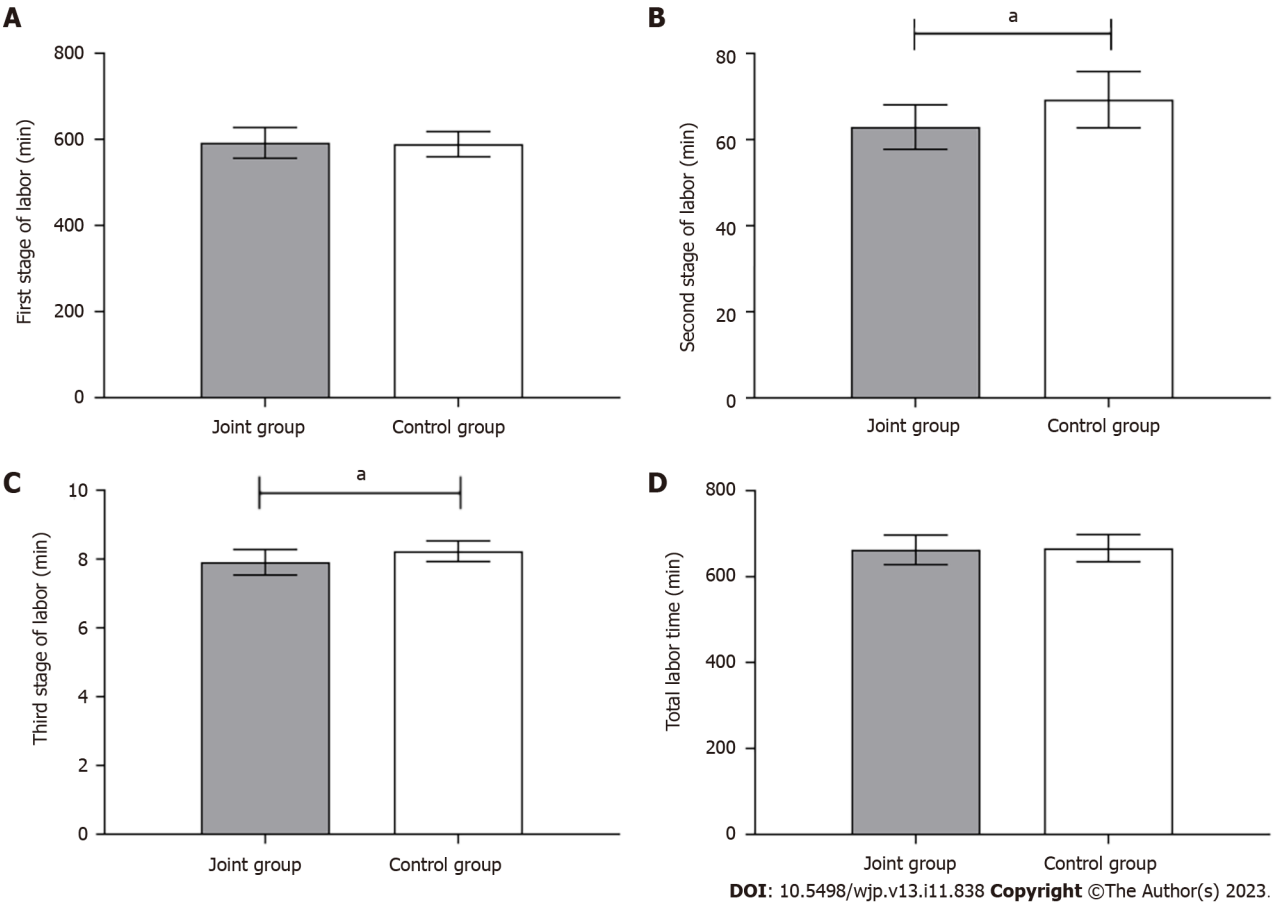
Comparison of motor block effects between the two groups: The Bromage grade did not substantially differ between the two groups ($P > 0.05$) (Table 3). Comparison of complication rates between the two groups. The complication rates between the two groups did not differ significantly ($P > 0.05$) (Table 4).

Table 3 Comparison of the motor block effect between the two groups

Group	*n*	Grade 0	Grade 1	Grade 2	Grade 3
Joint group	60	52	7	1	0
Control group	60	46	9	4	1
Z value		2.277			
P value		0.131			

Table 4 Comparison of complication rates between the two groups (cases, %)

Group	Joint group	Control group	χ^2	*P* value
n	60	60		
Hypotension	0	1		
Nausea and vomiting	2	1		
Pruritus	0	1		
Deceleration of fetal heart rate	0	1		
Total incidence	3.33 (2)	6.67 (4)	0.702	0.402



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Figure 3 Comparison of labor duration between the two groups. A: Comparison of the first stage of labor between the two groups; B: Comparison of the second stage of labor between the two groups; C: Comparison of the third stage of labor between the two groups; D: Comparison of the total stage of labor between the two groups. $^aP < 0.05$, comparison with the joint group.

DISCUSSION

Labor pain refers to the pain caused by strong uterine contractions, pelvic floor muscle expansion, and contraction of uterine tissue. Relevant studies have pointed out that intense and sustained pain during natural labor can directly lead to the occurrence of postpartum depression[12]. Hence, it is important to explore a better method of pain relief during labor. Specifically, optimal pain relief during labor can make pain relief easy to control, which is conducive to the smooth progress of labor. Continuous epidural block has been widely used internationally, with exact analgesic effects, lasting effects, little influence on circulation, and no side effects or complications of general anesthesia, such as changes in consciousness, hypoxia, hypercapnia, or aspiration[13]. Previous studies have shown that combined spinal-epidural anesthesia can reduce the pain of women during natural childbirth[14]. Intravertebral analgesia is currently considered by most scholars to be the most effective labor analgesia method. This method can effectively reduce pain during uterine contraction, reduce the stress response during labor, and contribute to the stability of the internal environment of the parturient and the smooth recovery of the body in the postpartum period[15]. The current study revealed that the VAS scores during the first, second, and third stages of labor were lower in the joint group than in the control group, suggesting that combined spinal-epidural anesthesia could alleviate labor pain for women during natural labor, which was consistent with the above research results. However, it should be noted that although combined anesthesia reduces the degree of labor pain, the analgesic drugs used will still have varying degrees of impact on the mother and child, and analgesic drug use during labor can easily hide excessive contractions and can also lead to contraction inhibition. Hence, it is necessary to choose the appropriate delivery method according to the patient's condition. Moreover, the outcomes of the present research demonstrated lower rates of conversion to cesarean section and postpartum blood loss in the joint group than in the control group, suggesting that combined anesthesia can promote the smooth progress of natural delivery. Because pain during labor can be alleviated, a series of physiological changes caused by labor pain can be relieved, and maternal fear and tension can be alleviated, which is conducive to the smooth progress of labor and indirectly reduces the rate of cesarean section[16].

Childbirth is a complex physiological and psychological process that is affected by mental, psychological, and environmental factors. Fear-tension-pain syndrome is common in parturient women. Due to a lack of understanding of the delivery process, an abnormal pregnancy history, existing mental and psychological disorders, and endocrine changes during childbirth, parturient women, especially primiparous parturient women, experience negative emotions such as fear, tension, anxiety, and depression, which are different from those in nonpregnancy[17]. According to literature reports, approximately 5% of the normal population has anxiety, and the incidence of prenatal anxiety can reach 8%-16.5%[18]. Childbirth self-efficacy refers to the belief or confidence that one can apply some techniques to manage and reduce pain during labor. According to some studies, the threshold of childbirth pain for women with poor mental health is reduced, and the psychological advantages generated by the participation of parturients in analgesia can eliminate the tension and anxiety caused by childbirth, increase their self-confidence, reduce the rates of dystocia and childbirth complications, and create favorable conditions for ensuring the safety of the mother and child during childbirth[19]. In the present study, it was found that the SAS score was decreased and the GSES score was increased in the postpartum period in the joint group, implying that the combined spinal-epidural anesthesia improved the sense of self-efficacy and reduced the degree of anxiety. Therefore, medical workers need consider parturients are a whole, determine their mental state in a timely manner, choose safe, rapid, effective, and appropriate analgesic methods, and implement individualized treatment for parturients to achieve ideal labor analgesia. For parturients with low anxiety and depression levels, psychotherapy can be used to comfort them by addressing doubts, relieving tension and loneliness and enhancing maternal confidence in giving birth. In addition, the durations of the second and third stages of labor in the joint group were slightly decreased compared to those in the control group, indicating that combined spinal-epidural anesthesia could reduce the duration of labor in women with natural delivery, which may be related to the reduction of labor pain and anxiety by combined anesthesia.

Umbilical cord blood gas is affected not only by the process of labor but also by placental function, umbilical cord factors, and maternal blood gas status. According to relevant reports, abnormal blood gas indices of cord blood are related to maternal emotions in addition to labor pain[20]. During childbirth, appropriate tension and anxiety can improve a mother's ability to adapt to the environment, which can be accompanied by activation of the sympathetic nervous system. Increased catecholamines acting on α receptors constrict peripheral blood vessels, increase the heart rate, redistribute cardiac output, and ensure the supply of vital organs such as the heart and brain, making up for the shortage of the maternal supply and improving the fetus's tolerance to hypoxia; however, excessive anxiety can affect umbilical cord blood hemodynamics, leading to fetal hypoxia[21,22]. Since the above research results showed that combined anesthesia can help to reduce patients' anxiety, the author believes that this anesthesia method can improve umbilical artery blood gas indices. In the present research, no significant differences were seen in pH, PO_2, PCO_2, and BE between the joint group and the control group, indicating that combined spinal-epidural anesthesia and single epidural anesthesia had little impact on the umbilical artery blood gas indices in parturients who gave birth naturally, which is inconsistent with the relevant research results[23]. This might be due to the study's small sample size; thus, the sample size should be increased for further analysis.

Experiencing high levels of tension, anxiety, and intense pain during labor can trigger a cascade of neuroendocrine reactions within the body. This can lead to elevated levels of catecholamines and adrenal corticosteroids in the bloodstream, resulting in increased oxygen consumption, heightened cardiac burden, uterine vasoconstriction, decreased blood flow, fetal distress, and potential uterine inertia. Pain can cause hyperventilation in parturients, which has adverse effects on their cardiovascular, endocrine, and psychological conditions and can increase the incidence of uterine inertia and uncoordinated uterine contraction. The current study demonstrated that Cor, ADR, and NO levels were comparatively lower in the joint group than in the control group, implying that the combination of lumbar and epidural

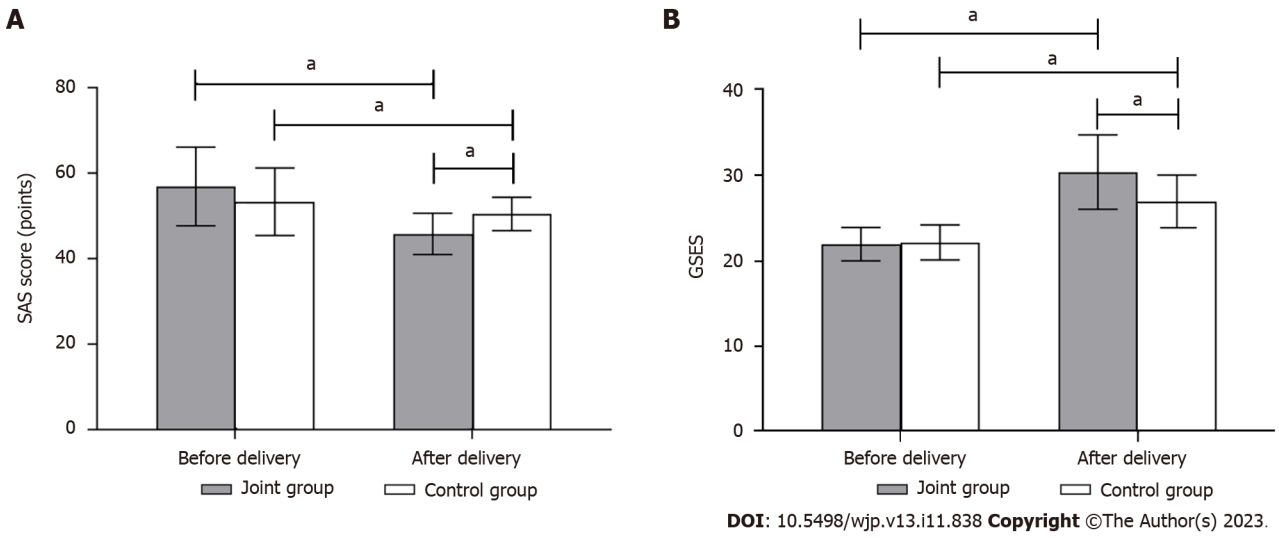


Figure 4 Comparison of anxiety and depression between the two groups. A: Comparison of Self-rating Anxiety Scale score between the two groups; B: Comparison of General Self-Efficacy Scale between the two groups. [a]*P* < 0.05, comparison with the joint group. SAS: Self-rating Anxiety Scale; GSES: General Self-Efficacy Scale.

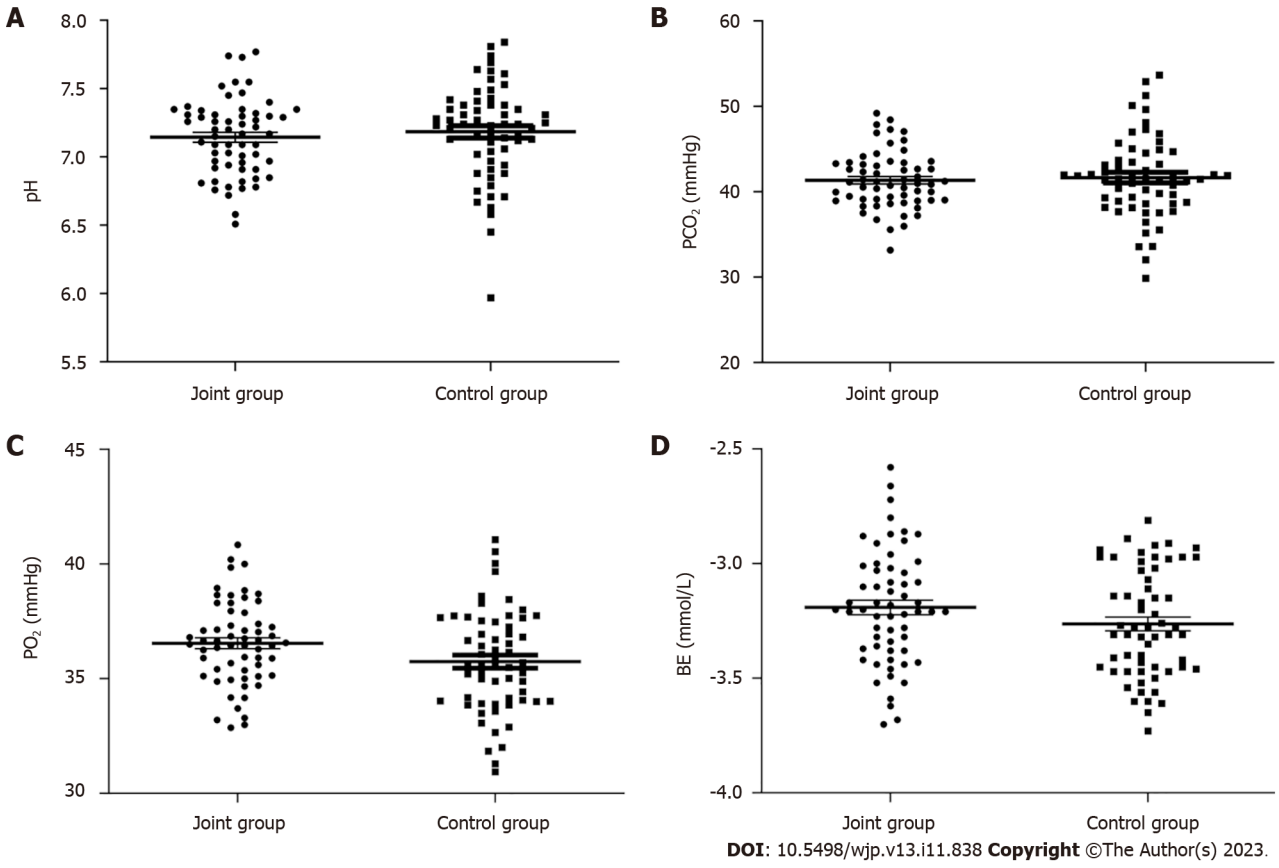
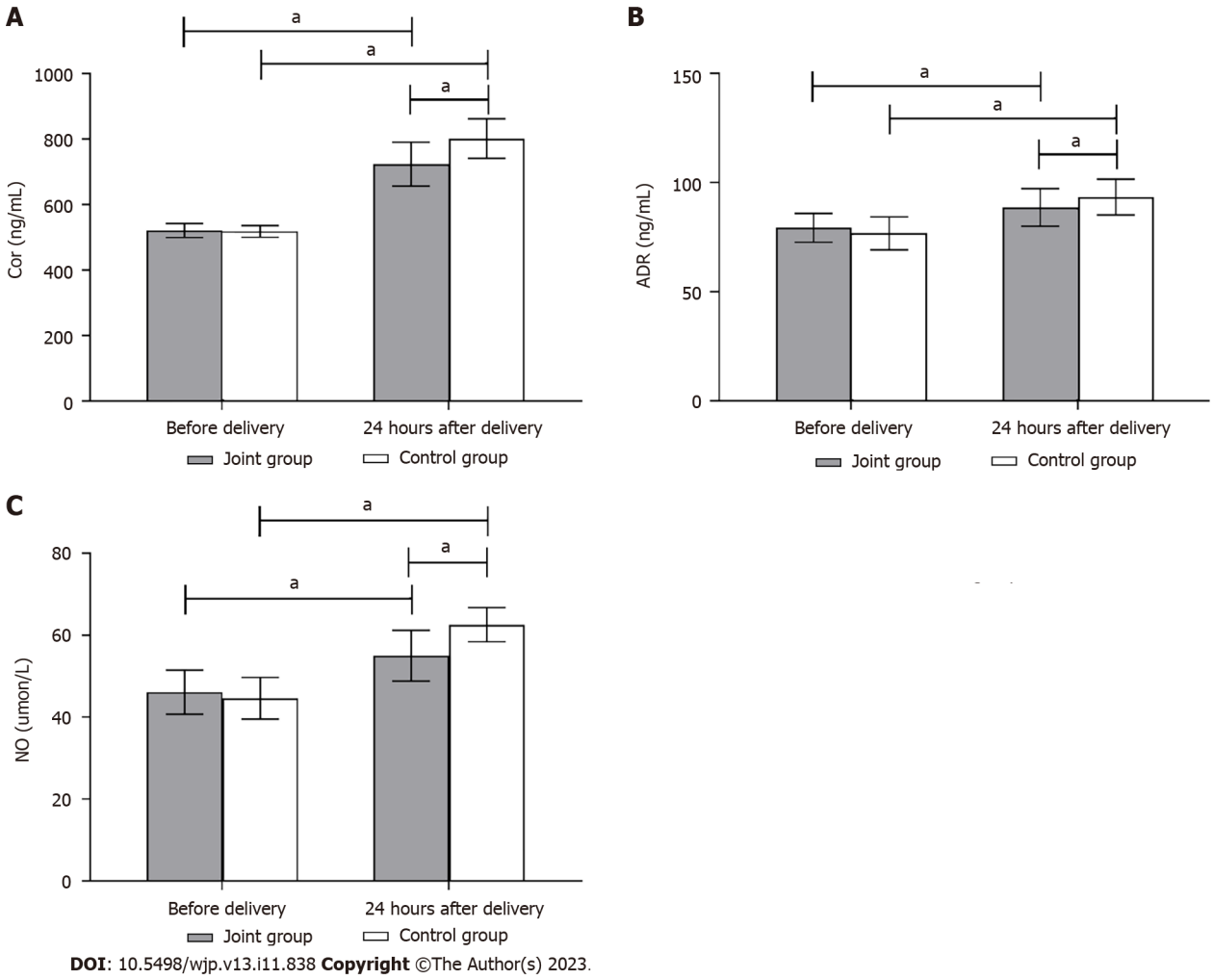


Figure 5 Comparison of blood gas analysis indices of the umbilical artery between the two groups. A: Comparison of pH value between the two groups; B: Comparison of pCO_2 value between the two groups; C: Comparison of pO_2 value between the two groups; D: Comparison of BE value between the two groups.

anesthesia could reduce the postoperative stress level of the body, which was largely associated with the reduction in postoperative pain and improvement in negative emotions of the women in the combined anesthesia group. Related research demonstrates that the degree of motor block can be reduced by giving combined spinal-epidural anesthesia to women during natural childbirth[24]. Nevertheless, no significant differences were found in the Bromage grade or complication rate between the two groups, indicating that combined anesthesia and epidural block alone had little effect on motor block. The reason for this remains unknown, so further analysis should be conducted.



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Figure 6 Comparison of stress indices between the two groups. A: Comparison of cortisol value between the two groups; B: Comparison of adrenaline value between the two groups; C: Comparison of nitric oxide value between the two groups. $^{a}P < 0.05$, comparison with the joint group. Cor: Cortisol; ADR: Adrenaline; NO: Nitric oxide.

CONCLUSION

Combined spinal-epidural anesthesia for women during natural labor can reduce anxiety, ease pain, shorten the labor time, and reduce the postoperative stress level of the body, but did not result in a motor block. This study shows that, in addition to improving the method of anesthesia, prenatal education should also be carried out. By fully providing knowledge on labor and labor pain, prenatal education can help parturients understand how to judge labor pain, which is conducive to improving continuous muscle tension and enhancing the analgesic effect for painless labor.

ARTICLE HIGHLIGHTS

Research background

The background of this study is that the rate of natural childbirth is increasing, the rate of cesarean section is decreasing, and anesthesia and analgesia in natural childbirth are getting more and more clinical attention. The significance of this study is to explore new methods of anesthesia and analgesia in natural childbirth.

Research motivation

The main topic of this study is anesthesia and analgesia for natural parturients, and it is necessary to explore more effective anesthesia and analgesia methods for natural parturients. The significance of this study is to confirm the effectiveness of combined spinal-epidural anesthesia in the analgesia of women in natural childbirth, and encourage clinical teams to continue to explore more effective analgesia methods for women in natural childbirth.

Research objectives

The purpose of this study was to compare the analgesic effect of different analgesic methods on women in natural childbirth, and to observe the analgesic advantage of combined spinal-epidural anesthesia on women in natural childbirth. It was found that the combined spinal-epidural anesthesia can effectively improve the labor pain, shorten the labor process, relieve the bad mood and reduce the postoperative stress of the parturients. To provide a new reference for the analgesia of parturients in clinical natural labor in the future.

Research methods

In this study, the pregnant women were divided into two groups by randomized control method, and the general data, pain degree, newborn condition, self-efficacy, umbilical artery blood gas analysis index, stress index and movement blocker complications of the two groups were statistically analyzed by independent sample *t* test, paired sample *t* test and χ^2 test.

Research results

Combined spinal-epidural anesthesia has a more significant effect on the improvement of labor pain in women with natural delivery, with significant improvements in labor pain, cesarean section rate, blood loss, adverse emotions, stress reaction and other aspects, providing a new analgesic method for women with natural delivery. Further large-scale studies are needed to verify the effectiveness of this method.

Research conclusions

The bad mood of natural childbirth women can affect the pain threshold of women, making them more sensitive to pain, and pain strengthens the bad mood of women, affecting childbirth. Therefore, we should pay attention to the influence of analgesic methods on maternal bad mood. Combined spinal-epidural anesthesia has good analgesic effect on parturients in natural labor.

Research perspectives

Natural childbirth women should not only consider the outcome of childbirth, but also pay attention to the personal state of the mother during childbirth. Future research aims to further explore the effects of analgesia on maternal adverse mood and stress response.

FOOTNOTES

Author contributions: Cai L and Cao S initiated the project and designed the experiment; Jiang JJ conducted clinical data collection; Cai L and Jiang JJ performed postoperative follow-up and recorded data; Wang TT conducted a number of collation and statistical analysis; Cai L wrote the original manuscript; Cao S revised the paper; and all authors have read and approved the final manuscript.

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Data sharing statement: All data generated or analyzed during this study are included in this published article.

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ORIGINAL ARTICLE

Retrospective Study

Clinical application of multidisciplinary team- and evidence-based practice project in gynecological patients with perioperative hypothermia

Qing-Yan Liu, Tong-Yang You, Dai-Ying Zhang, Juan Wang

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Abstract

BACKGROUND

Perioperative hypothermia (PH) negatively affects the physical and mental health of patients to varying degrees. Currently, there is no effective multidisciplinary team (MDT) intervention for gynecological patients with PH.

AIM

To apply the best evidence on the prevention and management of PH in gynecological patients, improve the quality of perioperative evidence-based care based on treatment by an MDT for gynecological patients and analyze the effect of MDT- and evidence-based practice (EBP) projects on the psychological status and cognitive function of gynecological patients with PH.

METHODS

Under the guidance of knowledge translation and combined with the opinions of involved stakeholders and clinical experts, the best evidence for PH prevention and management in gynecological patients was selected and adjusted to suit the practice setting. Based on the evidence, the practice plan was developed, and the MDT intervention was carried out in the preoperative ward, the preoperative preparation room, the intraoperative operating room, the postanesthesia care unit, and the 24-hour postoperative gynecological ward through the EBP program. The incidence of hypothermia, the nurses' awareness, the implementation rate of examination indicators, and the thermal comfort level, psychological status and cognitive function of patients were compared before and after the implementation of the program.

RESULTS

The incidence of PH in gynecological patients decreased from 43.33% to 13.33% after the implementation of the scheme. The implementation rate of examination

indicators 6-10, 12, 14, 16-18, 21, and 22 reached 100%, and that of other indicators was above 90%, except for examination indicators 5 and 13, which was 66.67%; the indices were significantly improved compared with the baseline (before evidence application) ($P < 0.05$). The score of nurses' awareness of PH prevention and management in gynecological patients increased from 60.96 ± 9.70 to 88.08 ± 8.96, and the difference was statistically significant ($P < 0.001$). The total score of the perioperative thermal comfort level of patients undergoing gynecological surgery was 27.97 ± 2.04, which was significantly increased compared with the score of 21.27 ± 1.57 observed by researchers at baseline ($P < 0.001$). The perioperative Hamilton Depression Scale and Hamilton Anxiety Scale scores of patients undergoing gynecological surgery decreased from 15.03 ± 3.16 and 13.93 ± 2.64 to 4.30 ± 1.15 and 3.53 ± 0.78, respectively, with statistically significant differences ($P < 0.001$). The perioperative Montreal Cognitive Assessment Scale score of the gynecological surgery patients increased from 23.17 ± 1.68 to 26.93 ± 1.11, also with statistical significance ($P < 0.001$).

CONCLUSION

MDT-based EBP for PH prevention and management in gynecological patients during the perioperative period can standardize nursing operations, improve nurses' awareness and behavioral compliance with gynecological hypothermia management, and reduce the occurrence of PH in gynecological patients while playing a positive role in reducing patients' negative emotions and enhancing their cognitive function.

Key Words: Hypothermia; Gynecology; Evidence-based care; Knowledge translation; Multidisciplinary team

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Core Tip: At present, there is a lack of effective measures for perioperative hypothermia (PH) management in gynecological patients in China. This study verified the effectiveness of evidence-based practice project based on multi-disciplinary team in PH management of gynecological patients from the aspects of incidence of hypothermia, nurses' awareness, implementation rate of examination indicators, and the thermal comfort level, psychological status and cognitive function of patients.

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INTRODUCTION

Perioperative hypothermia (PH) refers to the phenomenon in which the body's core temperature is lower than 36 °C for various reasons in surgical patients[1] and has a high incidence. PH can delay the action time of anesthetic drugs, trigger unexpected events such as respiratory depression, vomiting and chills, and increase postoperative cardiovascular system complications, postoperative infection risk, coagulation dysfunction and other adverse consequences[2], prolonging the hospitalization time of surgical patients, increasing their hospitalization medical expenses and economic burden, and reducing social satisfaction[3]. Due to preoperative transfer, intraoperative anesthesia, the use of large amounts of flushing fluid, and the placement of patients in special positions, the incidence of PH in gynecological patients in China ranges from 31.3% to 65%[4,5], which is high, and the incidence in postanesthesia care units (PACUs) reaches 22.0%[6], necessitating improvement. The prevention and management of PH in gynecological patients is the responsibility of the multidisciplinary team (MDT)[7]. At present, the foreign practice guidelines and evidence summary on PH prevention and management are relatively comprehensive and mature. In contrast, although there are relevant studies and evidence on PH in China, none of them have been carried out according to the characteristics of gynecological patients, nor have they been effectively applied to clinical practice in China, resulting in a substantial difference between practice and evidence. In addition, there is no MDT intervention to improve the status quo of PH in patients. All these factors can explain the high incidence of PH in gynecological patients in China.

Knowledge translation (KT) refers to studying how to apply research evidence or clinical practice guidelines based on research evidence to clinical practice. The Knowledge-to-Action (KTA) framework, the most commonly used in KT theoretical frameworks, divides the KT process into knowledge creation and knowledge application, promoting the synthesis, dissemination and application of knowledge. The KT framework is a dynamic process through which knowledge producers (*i.e.*, researchers) and knowledge applicators (*i.e.*, practitioners) are integrated in a cooperative and interactive manner, reflecting a complete cycle from knowledge creation to application and providing a clear conceptual framework for the translation of knowledge into practice[8]. The application of an MDT under the guidance of KT may be of great help to the management of PH in gynecological patients. The MDT model of diagnosis, treatment and care has been shown to be one of the important models in medicine worldwide, which emphasizes patient-centered, curative effect-oriented, and evidence-based medicine to provide patients with all-round, personalized, refined, effective and

reasonable medical services[9]. MDT management has been shown to effectively improve the quality of life of patients with gynecological malignancies[10], promote their rapid recovery[11], and enhance the comprehensive ability of gynecological nurses[12]. To effectively prevent and manage the occurrence of PH in gynecological patients, the MDT-based evidence-based practice (EBP) project applies the best evidence scheme for the prevention and management of PH in gynecology, providing new ideas for solving the problem of PH in gynecological patients.

MATERIALS AND METHODS

Presentation of clinical problems

Based on a literature review and clinical practice, the clinical question "How can the incidence of PH be reduced in gynecological patients?", was identified and transformed into evidence-based problems according to the Population, Intervention, Control, and Outcome approach: (1) Population: Adult patients (≥ 18 years old) who underwent gynecological surgery (laparoscopy/hysteroscopy/Laparotomy) for 2 h or more; (2) Intervention: Prevention and management strategies of unplanned PH; (3) Control: Clinical routine nursing measures; and (4) Outcome: The implementation rate of examination indicators, nurses' awareness scores, incidence of hypothermia in gynecological patients, standardized procedures for PH prevention and management in gynecological patients, and psychological status and cognitive function of gynecological patients.

Construction of an evidence-based group

The team consisted of 9 members, including 2 operating room head nurses, 1 head nurse in the anesthesiology department, 1 head nurse in the gynecology department, 3 floor nurses, and 2 postgraduate students. Among them, the operating room head nurses were responsible for the overall research design and guidance; the postgraduates were responsible for evidence extraction, baseline review, data collection and analysis; and the remaining team members were responsible for nurse training, organization and coordination, and quality supervision.

Evidence acquisition

In this study, relevant clinical practice guidelines, expert consensus, evidence summaries and systematic reviews were retrieved from databases such as PubMed/Medline, JBI's Evidence-based Practice Database, the Cochrane Library, National Institute of Health and Care Excellence, Registered Nurses Association of Ontario, OVID, Science Direct, Association of the Scientific Medical Societies in Germany (AWMF), Association of Operating Room Nurses, China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, and Chinese BioMedical Literature Database from 2000 to April 2021. Of the 592 documents retrieved, 7 articles were included after reading the abstracts and full texts and evaluating the literature quality, including 2 guidelines[13,14], 2 expert consensuses[2,15], and 3 systematic reviews[16-18]. For the guidelines included, the quality was quantitatively evaluated using the Appraisal of Guidelines for Research and Evaluation instrument II[19], and the results are shown in Table 1. The Assessment of Multiple Systematic Reviews score[20] was used for quality assessment of the systematic reviews included, with the results presented in Table 2. For expert consensus, the quality was assessed by referring to JBI's critical appraisal tools[21]; the evaluation results of all the other items of the two articles were "Yes" except Item 6, "Are there any inconsistencies between all the proposed opinions and previous documents?" The research design of the included articles was complete, and the overall quality was high, which met the inclusion criteria. A total of 26 pieces of relevant evidence were obtained through the included studies, as shown in Table 3.

Selection of evidence suitable for clinical settings

The KTA model emphasizes the appropriate selection of evidence to suit specific clinical scenarios[8] and the adjustment of evidence with the input of stakeholders. In this study, 16 nurses and doctors from different departments (operating room, department of gynecology, and department of anesthesiology) with different academic qualifications and working years were selected as stakeholders by purposive sampling to select evidence suitable for clinical settings. Then, the stakeholders selected and adjusted evidence from the aspects of applicability, suitability, effectiveness and clinical significance. According to the opinions of the involved stakeholders, the applicability of heating humidification for oxygen inhalation was not considered feasible, so the evidence "to provide heated and humidified oxygen therapy for patients" was deleted (see Table 4 for the final included evidence).

Identification of gaps between evidence and clinical practice

To introduce evidence into clinical practice, this study evaluated the readiness of EBP. According to the evidence introduced into clinical practice, a total of 23 examination indicators were used as the evaluation criteria to investigate the current status of evidence application for PH prevention and management in gynecological patients in the pilot wards. The research subjects and examination methods are shown in Table 4. The review was jointly completed by the researcher and another member of the research team. Before the review, the examination contents and evaluation methods were further confirmed with the research team to ensure consistency. Except for indicators 1, 10, 12, 18, and 19, the implementation rate of other indicators was less than 50%, with the implementation rate of indicators 4 and 22 even being 0, suggesting the need to improve the completion of evidence implementation by medical staff. Therefore, this study investigated the awareness of relevant medical staff in the pilot wards on the prevention and management of PH in gynecological patients. A self-designed questionnaire was developed based on the evidence content to assess nurses' knowledge

Table 1 Quality evaluation results of the included guidelines

Ref.	Percentage of standardization in various fields						Number of domains ≥ 60% (*n*)	Number of domains ≥ 30% (*n*)	Recommended level
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence			
Torossian *et al*[13]	100	88.89	79.17	100	68.75	62.5	6	6	A
Hooper *et al*[14]	88.89	52.78	62.5	80.56	43.75	20.84	3	5	B

Table 2 Quality evaluation results of the included systematic reviews

Indicators	Galvão *et al* [17]	Moola and Lockwood [18]	Wang and Mao [16]
Was an "a priori" design provided?	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	Yes	Yes	Yes
Was a comprehensive literature search performed?	Yes	Yes	Yes
Was the status of publication used as an inclusion criteria, such as grey literature?	No	Yes	No
Was a list of studies provided?	Yes	Yes	Yes
Were the characteristics of the included studies provided?	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes
Was the likelihood of publication bias assessed?	No	No	Yes
Was the conflict of interest stated?	Yes	Yes	No

level (20 items for hypothermia identification, assessment, prevention, treatment and health education domains, with 2.5 points for each item) and practice level (10 items for the aspects of attitude and awareness of the prevention and management of PH in gynecological patients, with 5 points for each item), with a total score of 100 points. A total of 49 nurses in the pilot wards were enrolled, and the inclusion criteria were as follows: (1) Working in the department for more than 2 years; and (2) Voluntary participation in this study. The awareness of nurses regarding PH prevention and management in gynecological patients was 60.96 ± 9.70 points, which was at the medium level.

Development of MDT-based EBP project

Based on the evidence content, the investigation results of the implementation of the examination indicators in the pilot wards and the awareness of the associated medical staff, as well as the "Promoting Action on Research Implementation in Health Services Integrated Framework (i-PARIHS)"[22], semistructured interviews were conducted among nurses from different wards with different seniority levels to identify barriers and facilitators for the implementation of the protocol. After the formulation of action strategies, the evidence-based team developed an EBP project for PH prevention and management in gynecological patients, compiled a manual of relevant surgical education and knowledge, developed a thermal comfort rating scale, and unified the comprehensive thermal insulation methods and procedures for gynecological surgery patients. After the formation of the scheme, the evidence-based team discussed the comprehensiveness and clinical feasibility of the scheme item by item with the hospital management team members and nine experts with extensive perioperative nursing experience in gynecology, and the program was unanimously recognized.

EBP program application and effect evaluation

Practice site: The EBP program of this study was conducted in the operating room and gynecology and anesthesiology departments of a grade III-A hospital in Sichuan Province, with a total of 49 nurses participating (see 1.5 for the inclusion criteria).

Implementation of the EBP project: The EBP project was implemented from August to October 2021. The KTA model notes that to promote changes in practice, effective action strategies should be developed according to the barriers to evidence application. This study drew on the i-PARIHS framework to analyze the barriers and facilitators in the application of evidence for the prevention and management of PH in gynecological patients in pilot wards, with the

Table 3 Contents of the best evidence

Stage	Evidence
Preoperative ward	To educate patients on thermal insulation and matters needing attention before surgery
	To measure and record the patient's axillary temperature before surgery
	To actively warm patients whose body temperature is below 36°C to 36°C and keep the patient warm during transfer
Preoperative preparation room	To assess the risk factors for hypothermia in patients
	To use a temperature monitoring equipment to measure and record the patient's body temperature before anesthesia induction
	To preheat 10-30 min before anesthesia induction
	To use carbon fiber heating wire to actively and continuously warm patients with body temperature below 36°C to above 36°C
	To maintain the operating room temperature no less than 24°C, and to lower the temperature only when active heating is established
Intraoperative operating room	To adopt an effective comprehensive thermal insulation strategy after anesthesia and maintain the axillary temperature at least 36.5°C
	To expose the surgical area and cover the rest for thermal insulation
	The infusion pipeline is continuously heated to 37°C if the intravenous infusion volume is more than 500ml.
	To heat the washing solution with a thermostatic chamber to 38-40°C
	To perform continuous intraoperative monitoring and recording every 15 min
	To evaluate intraoperative risk factors and hypothermia symptoms and signs
Postanesthesia care unit	To measure the body temperature and record it every 15 min. Passive insulation is adopted if there is no hypothermia. Monitoring site: armpit
	To adjust the PACU ambient temperature to 24°C
	To evaluate the patient's thermal comfort level
	To actively warm patients whose body temperature is below 36°C to above 36°C
	To heat the intravenous fluids
	To provide heated and humidified oxygen therapy for patients
	To transfer the patient out of PACU only when her body temperature is ≥ 36°C
24-hour postoperative gyneco-logical ward	To measure, monitor and record the body temperature every 4 h
	To cover to keep warm
	To educate family members thermal insulation methods: blankets, socks, clothes, raising the ambient temperature, hot water, *etc*.
	To continuously and actively warm patients below 36°C until they feel warm and comfortable, and to monitor and record every 30 min
	To evaluate the patient's thermal comfort level
	To pay close attention to patients' psychological changes, perceive their potential negative emotions such as anxiety and depression, and give timely relief and comfort
	To patiently answer any problems that may cause psychological distress to patients, and help them establish a positive attitude

PACU: Postanesthesia care unit.

results presented in Table 5. According to the barriers and the actual situation in the wards, the following action strategies were developed for the smooth implementation of the EBP project.

Effect evaluation: The research participants consisted of 16, 13, and 20 nurses from the gynecological operating room, anesthesiology department, and gynecology department, respectively, as well as 60 patients undergoing gynecological surgery (inclusion criteria: Age ≥ 18 years; operation time ≥ 2 h; good cognitive and responsive skills; voluntary participation in this study). The effect of the EBP project was evaluated by a controlled before-and-after trial among nurses and a nonconcurrent control trial among patients.

Table 4 Relationship between evidence, practice protocol related documentation and examination indicators

Stage	Evidence suitable for clinical scenarios	Practice protocol related documentation	Examination indicators	Examination objectives and methods
Preoperative ward	To educate patients on thermal insulation and matters needing attention before surgery	Manuals and videos of perioperative health education (patient edition)	The operating room has propaganda materials on hypothermia prevention and management	Department: Document consultation
			Checking the preoperative follow-up sheet of gynecological surgery patients	Medical staff: Document consultation and observation
	To measure and record the patient's axillary temperature before surgery	Surgical patient handover/transfer proforma	Checking the surgical patient handover/transfer proforma	Medical staff: Document consultation and observation
	To actively warm patients whose body temperature is below 36°C to 36°C and keep the patient warm during transfer	Hypothermia emergency procedures	The operating room has a hypothermia emergency process to ensure continuous heat preservation during patient transfer	Medical staff: Document consultation and observation
Preoperative operating room	To assess the risk factors for hypothermia in patients	Hypothermia risk factor evaluation sheet	The operating room has an evaluation sheet to evaluate the risk factors of hypothermia in patients	Operating Room: document consultation
	To use a temperature monitoring equipment to measure and record the patient's body temperature before anesthesia induction	Procedure for the use of temperature monitoring equipment	Before anesthesia induction, a temperature monitoring equipment is used for patients with operation duration of 2h or longer	Medical staff: Observation and document consultation
	To actively warm patients whose body temperature is below 36°C to above 36°C	Active heat preservation methods for hypothermia patients	Effective warming strategies are taken for hypothermia patients	Medical staff: Observation and document consultation
	To preheat 10-30 min before anesthesia induction	Pre-heat preservation methods	10-30 min of pre-heat preservation is performed on gynecological patients before anesthesia induction	Medical staff: Observation
	To maintain the operating room temperature no less than 24°C, and to lower the temperature only when active heating is established	-	The operating room ambient temperature is adjusted to 24°C and above before surgery	Medical staff: Observation
Intraoperative operating room	To adopt an effective comprehensive thermal insulation strategy after anesthesia and maintain the axillary temperature at least 36.5°C	Intraoperative comprehensive thermal insulation strategies (active and passive thermal insulation, blood transfusion and infusion warming, continuous dynamic monitoring of body temperature, *etc.*)	According to the probability of hypothermia in gynecological patients during operation, a corresponding comprehensive heat preservation strategy is selected to maintain the axillary temperature of the patient at least 36.5°C	Medical staff: Observation, document consultation
	To expose the surgical area and cover the rest for thermal insulation	-	The surgical area is exposed and the rest is covered for thermal insulation	Medical staff: Observation
	To warm the intravenous fluid or blood transfusion with a warming device to 37°C if the amount was ≥ 500 mL	Procedure for the use of infusion pipeline heating instrument	The infusion pipeline was warmed for those with a intravenous fluid or blood transfusion volume ≥ 500 mL	Medical staff: Observation
	To heat the intraoperative washing solution with a thermostatic chamber to 38-40°C	-	The washing solution is used at 38-40°C	Medical staff: Observation
	To continuously monitor and record the patient's body temperature once every 30 min intraoperatively, and to record it once every 15 min during recovery from anesthesia	-	The body temperature is continuously monitored and recorded on time intraoperatively	Medical staff: Observation, document consultation
	To evaluate hypothermia symptoms and signs during the operation	Evaluation methods of symptoms and signs of hypothermia in patients during operation	The patient is observed for symptoms and signs of hypothermia during the operation	Medical staff: Observation
PACU	To measure the body temperature and record it every 15 min. Passive	Active insulation methods and temperature handover record for	The patient's temperature is measured and the hypothermia patients are	Medical staff: Observation,

	thermal insulation is adopted for those without hypothermia, and active thermal insulation is taken to above 36°C for those below 36°C	hypothermia patients	warmed effectively, and the temperature handover record is established	document consultation
	To adjust the PACU ambient temperature to 24°C	-	The PACU temperature is adjusted to 24°C and above	Medical staff: Observation
	To send the patient back to the ward when the body temperature is not lower than 36°C	-	The patient is transferred out from the PACU only when the body temperature is ≥ 36°C	Medical staff: Observation, document consultation
24-hour postoperative gynecological ward	To monitor and record the patient's axillary temperature every 4 h	-	The patient's axillary temperature is measured and recorded every 4 h	Medical staff: Observation, document consultation
	To cover to keep warm	-	The patient is covered to keep warm	Medical staff: observation
	To teach the patient's family how to keep warm effectively	Health education handbook	The patient's family members' are informed of effective thermal insulation methods	Medical staff: Observation and questioning
	To continuously and actively warm patients below 36°C until they feel warm and comfortable, and to monitor and record every 30 min	Active heat preservation methods for hypothermia patients	The hypothermia patients are continuously and actively warmed, with their body temperatures monitored and recorded every 30 min	Medical staff: Observation, document consultation
	To evaluate the patient's thermal comfort level	Thermal comfort rating scale	The patient's thermal comfort level is assessed	Medical staff: Document consultation

PACU: Postanesthesia care unit.

Table 5 Barriers and action strategies for prevention and management of hypothermia in patients

Serial number	Obstacle	Action strategy
1	Nurses lack relevant knowledge and awareness of perioperative hypothermia management of gynecological patients	To hold special training to explain relevant knowledge to nurses with PPT combined with nursing knowledge handbook, and to explain various procedures and nursing norms through on-site demonstration and watching operation videos. To ensure that nurses in the operating room, anesthesiology department and gynecology department receive knowledge training on hypothermia prevention at least once every six months, and to assess them for knowledge and practice at least once a year after training
2	The contents of health education on the day before surgery vary greatly and lacks gynecological expertise	To formulate a preoperative education manual of gynecology specialty, and to push the preoperative education video for gynecological patients by WeChat official account
3	The lithotomy position is mostly commonly used posture in gynecological surgery, resulting in inadequate ankle and foot warmth. In addition, there is a lack of special thermal insulation equipment for the lithotomy position	To purchase lithotomy position-dedicated strip-shaped inflatable heating blankets, wrap the patient's legs with cotton pads, and use sterile leg covers to meet the warm-keeping requirements of patients undergoing surgery in the lithotomy position
4	There are communication barriers among multi-department nurses on the prevention and management of perioperative hypothermia in gynecological patients	To establish a perioperative hypothermia prevention and management group led by the head nurses who also play a key role in the practice reform, with operating room gynecological specialists, anesthesiology nurses, gynecological nurses as the team members and the head nurses of the three departments as the group leaders. To establish a WeChat exchange group to remind, supervise and control the quality in the preoperative ward, preoperative preparation room, intraoperative operating room and postoperative PACU. To listen to the feedback and suggestions of nurses and patients during field observation, and adjust and optimize the nursing process. The head nurse should report the practice changes to the evidence-based practice group every month, so as to discuss, analyze and solve the problems that arise
5	There is a lack of corresponding evaluation tools	To introduce the intraoperative hypothermia risk prediction model calculation software constructed by Professor Huang Yuguang to evaluate the hypothermia risk of patients, and to explain the checked contents. To self-develop a thermal comfort scale, and conduct unified training for medical staff

PACU: Postanesthesia care unit; PPT: Power point.

Outcome measures: (1) The implementation rate of examination indicators was as follows: The evidence suitable for clinical situations was converted into measurable and easy-to-assess quality examination indicators. If the examination indicators were correctly executed, they were marked with "√". Unimplemented or incorrectly implemented indicators were marked with "×". The percentage of correct implementations was calculated as the percentage of the number of correct implementations out of the total number of implementations; (2) The incidence of PH was evaluated as follows: The incidence of PH in 30 gynecological patients from April to June 2021 and another 30 gynecological patients from October 2021 to December 2021 was statistically analyzed; (3) The awareness level of nurses (gynecological operating room, anesthesiology department, and gynecology department) regarding PH prevention and management in gynecological patients was evaluated as follows: A self-designed questionnaire based on evidence content was used for assessment (see 1.5 for details); (4) The thermal comfort level of gynecological patients was investigated as follows: The operating room, PACU and gynecological ward patients were scored by the Visual Analog Scale. The scale has 10 items, with 10 points each and a full score of 30; (5) Psychological status was evaluated as follows: Patients' depression and anxiety were evaluated by the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA), respectively, whereby the HAMD score range was 0-68 and the HAMA score range was 0-56, both of which were directly proportional to depression and anxiety; and (6) Cognitive function was analyzed as follows: Patients' cognitive function was evaluated with the Montreal Cognitive Assessment Scale (MoCA; score range: 0-30). A score of 26 was considered normal, and a score less than 26 was indicative of cognitive function decline; in addition, the score was increased by 1 point if the patient's years of schooling was less than 12 years.

Data collection methods: Baseline review data were collected from April 2021 to June 2021, and data collection and analysis after program application were carried out from October 2021 to December 2021. A researcher followed up and observed the implementation of examination indicators and the occurrence of hypothermia on a daily and patient-by-patient basis and recorded it truthfully. (1) Document consultation: For indicators 1-7, 10, 14, 16, 18-19, and 22-23, the rules and regulations of the department, the relevant processes and the training records were checked; (2) Observation and questioning: For indicators 2-4 and 6-22, the "Checklist for Prevention and Management of Unplanned Hypothermia in Gynecological Surgery Patients" was formulated, and the nurses' implementation of the best evidence was evaluated through data analysis after clinical implementation; and (3) Questionnaire survey method: Based on the implementation of the examination indicators, a questionnaire on nurses' knowledge and practice was designed and prepared and distributed by the head nurse to the nurses to complete.

Statistical methods: SPSS 20.0 statistical software and Excel software were used for data entry and analysis. The quantitative data that conformed to a normal distribution are described by means ± standard deviations, and between-group comparisons were made by the *t* test; count data are described as frequencies and percentages, and chi-square tests were performed to identify differences between groups. All analyses relied upon a $P < 0.05$ statistical significance criterion.

RESULTS

General information

A total of 49 nurses (16, 13, and 20 nurses in the gynecological operating room, anesthesiology department, and gynecology department, respectively), including 44 females and 5 males aged 22-50 (32.1 ± 5.9) years, were investigated before and after the application of this scheme. Most of the nurses had bachelor's degrees (87.76%) and professional titles (67.35%). Thirty patients each were included before and after evidence application, and no significant intergroup differences were identified in terms of age, sex, length of hospital stay, education level, occupation, payment method of medical expenses, or operation duration ($P > 0.05$).

Incidence of hypothermia

The incidence of hypothermia among gynecological perioperative patients decreased from 43.33% to 13.33% after the application of the scheme, with statistical significance ($\chi^2 = 12.381$, $P < 0.001$).

Implementation rate of examination indicators

After the application of evidence, the implementation rate of examination indicators 6-10, 12, 14, 16-18, and 21-22 reached 100%; in addition to indicators 5 and 13 with an implementation rate of 66.67%, the implementation rate of other indicators was 90% or above. Except for indicators 10, 12, and 18, whose implementation rate had been 100% before evidence application, all the other indicators were significantly improved after evidence application ($P < 0.05$) (Table 6).

Nurses' awareness of PH prevention and management in gynecological patients

After the application of the EBP project, the nurses' awareness of PH prevention and management in gynecological patients increased from 60.96 ± 9.70 to 88.08 ± 8.96, with a statistically significant difference ($t = -29.866$, $P < 0.001$).

Perioperative thermal comfort level of patients undergoing gynecological surgery

The total score of the perioperative thermal comfort level of gynecological surgery patients was 27.97 ± 2.04 after the application of the EBP project, which was statistically significant compared with the score of 21.27 ± 1.57 established by

Table 6 Comparison of nurses' implementation of examination indicators before and after application of the evidence-based program

Examination indicators	Before evidence application (n = 30)			After evidence application (n = 30)			X^2	P value
	Implemented	Unimplemented	Implementation rate (%)	Implemented	Unimplemented	Implementation rate (%)		
Indicator 1	16	14	53.33	28	2	93.33	12.273	< 0.001
Indicator 2	15	15	50.00	29	1	96.67	20	< 0.001
Indicator 3	12	18	40.00	28	2	93.33	19.2	< 0.001
Indicator 4	0	30	0.00	27	3	90.00	49.091	< 0.001
Indicator 5	7	23	23.33	20	10	66.67	11.38	0.001
Indicator 6	15	15	50.00	30	0	100.00	20	< 0.001
Indicator 7	12	18	40.00	30	0	100.00	25.714	< 0.001
Indicator 8	15	15	50.00	30	0	100.00	20	< 0.001
Indicator 9	11	19	36.67	30	0	100.00	27.805	< 0.001
Indicator 10	29	1	96.67	30	0	100.00	1.017	0.313
Indicator 11	6	24	20.00	27	3	90.00	29.697	< 0.001
Indicator 12	28	2	93.33	30	0	100.00	2.069	0.15
Indicator 13	7	23	23.33	20	10	66.67	11.38	0.001
Indicator 14	3	27	10.00	30	0	100.00	49.091	< 0.001
Indicator 15	4	26	13.33	28	2	93.33	38.571	< 0.001
Indicator 16	14	16	46.67	30	0	100.00	21.818	< 0.001
Indicator 17	11	19	36.67	30	0	100.00	27.805	< 0.001
Indicator 18	30	0	100.00	30	0	100.00	-	-
Indicator 19	21	9	70.00	29	1	96.67	32.308	< 0.001
Indicator 20	12	18	40.00	28	2	93.33	19.2	< 0.001
Indicator 21	10	20	33.33	30	0	100.00	30	< 0.001
Indicator 22	0	30	0.00	30	0	100.00	60	< 0.001

researchers before the intervention (t = 13.693, P < 0.001).

Perioperative psychological status of patients undergoing gynecological surgery

The total score of the perioperative HAMD of gynecological surgery patients was 4.30 ± 1.15 after the application of the EBP project, which was statistically significant compared with the score of 15.03 ± 3.16 established by researchers before the intervention (t = 17.500, P < 0.001); the total HAMA score decreased from 13.93 ± 2.64 before the intervention to 3.53 ± 0.78 after the intervention, with statistical significance (t = 20.713, P < 0.001).

Perioperative cognitive function of patients undergoing gynecological surgery

The total MoCA score among gynecological surgery patients was 26.93 ± 1.11 after the application of the EBP project, which was statistically significant compared with the score of 23.17 ± 1.68 established by researchers before the

intervention (t = 10.226, P < 0.001).

DISCUSSION

The EBP project based on an MDT was scientific and feasible

A top-down literature search according to the "6S" retrieval model was conducted in this study, as well as rigorous study screening and quality evaluation. The quality evaluation results of the included documents were all high, which ensured the reliability of the evidence sources. To make the summarized evidence of MDT nursing of gynecological patients at different stages of the perioperative period feasible, appropriate, effective and clinically significant, this study followed the FAME principle and invited relevant stakeholders (clinical practitioners) from gynecology, anesthesiology and the operating room to participate in the evidence selection process, which enhanced the clinical practitioners' recognition of the evidence[23]. In addition, relevant experts were invited for consultation, and the clinical experience of clinical decision-makers, managers and practitioners was combined with the clinical evidence application sites, such as the operating room, gynecology and anesthesiology, so that the examination indicators were practical in clinical work. Moreover, based on continuous quality improvement advocated by the KT model and drawing on the i-PARIHS framework (which takes into account all issues that need to be considered, evaluated and planned in the process of evidence application and has been effectively applied in clinical practice as a theoretical framework to guide quality improvement and for the identification of prestudy barrier factors and facilitating factors[22]), this study analyzed the barriers and facilitators in the application of evidence related to the prevention and management of PH in gynecological patients in pilot wards. After determining the major barriers, action strategies were drawn up, and evidence-based intervention programs were formed. The whole process is standardized and scientific, which makes the EBP project scientific and feasible.

The MDT-based EBP project improved the implementation rate of examination indicators and enhanced nurses' awareness of hypothermia prevention and management

Based on the KT model, this EBP project transformed the evidence into clinical practice, formulated an intervention plan for PH prevention and management suitable for local gynecological surgery patients, and filled the relevant vacancies in the pilot operating room. Through the analysis of barriers, tailored action strategies were formed, contributing to the increase in the scores of ward nurses, operating room nurses and anesthesia nurses on PH prevention and management in gynecological patients from 60.96 ± 9.70 to 88.08 ± 8.96 and the increase in the examination indicator implementation rate from 0-100% to 66.67-100%, which was significantly improved compared with the values before evidence application (P < 0.05). This suggests that the EBP project enhanced the awareness of hypothermia prevention and management among nursing staff, especially gynecological nurses, and that most of the evidence was well applied in clinical practice. This may be related to the construction of practice plans, the implementation of action strategies and quality supervision, which clarified the job responsibilities and standardized the behavior of nurses, thus promoting changes in clinical practice, consistent with the results of a number of studies[24,25].

The EBP project based on an MDT reduced the incidence of PH in gynecological patients

The necessity and importance of the prevention and management of PH in surgical patients, an important part of operating room care, have been emphasized in the guidelines[13,14] when selecting the best evidence in this study. After the implementation of this EBP project, the incidence of PH in gynecological patients in the pilot wards decreased from 43.33% to 13.33%, and the score of perioperative thermal comfort level increased from 21.27 ± 1.57 to 27.97 ± 2.04, with statistical significance. It is suggested that the EBP project can effectively reduce the incidence of PH in gynecological patients and improve their thermal comfort level, similar to the findings of Xiao *et al*[26]. This may be related to the fact that this EBP project takes evidence-based evidence as the theoretical basis, implements patient-centered and multidisciplinary cooperation, and focuses on temperature management of gynecological patients throughout the perioperative period, including gynecology, operating room and PACU. The specific measures include giving health education about body temperature to patients and their families before and after surgery in gynecological wards; conducting preoperative hypothermia risk assessment and preinsulation in the operating room; using a lithotomy position-dedicated inflatable heating blanket during the operation according to the characteristics of commonly used lithotomy positions for gynecological patients, which can effectively cover the whole body of the patient with a better heating effect compared with the whole-body inflatable heating blanket in the supine position[27]; implementing comprehensive warm-keeping measures such as intravenous infusion and transfusion heating, lavage fluid heating and continuous body temperature monitoring; emphasizing continuous body temperature monitoring and passive thermal insulation when patients are in the PACU; performing temperature monitoring and active thermal insulation measures of abnormal hypothermia in the gynecological ward 24 h after surgery; and paying attention to the patient's thermal comfort level during the whole perioperative period. However, due to the short application time of evidence in this study and the small number of patients included, the effectiveness of this protocol needs validation through continuous application.

The EBP project based on an MDT improved the psychological status and cognitive function of gynecological patients during the perioperative period

In this study, the psychological status of gynecological patients during the perioperative period was evaluated by the HAMD and HAMA, and cognitive function was assessed by the MoCA. Before the implementation of the MDT-based

EBP project, gynecological perioperative patients suffered from varying degrees of negative emotions and cognitive impairment. Negative emotions such as anxiety and depression were significantly alleviated after the implementation of the MDT-based EBP project, and cognitive function was also significantly improved, mainly manifested in the significant reduction in HAMD and HAMA scores and the significant increase in MoCA scores. The above results suggest that the EBP project based on MDTs can effectively improve the psychological status and cognitive function of gynecological patients during the perioperative period. This may be attributed to the identification of potential psychological distress in perioperative gynecological patients and psychological interventions in the MDT-based EBP project. In addition to hypothermia prevention and thermal comfort intervention in the wards 24 h after surgery, the relevant members of the evidence-based team were also required to pay close attention to the psychological changes of patients and provide timely relief and comfort to minimize their negative emotions. At the same time, it is also necessary to give careful attention and patient answers to problems that may cause psychological distress to patients, which helps patients establish a positive psychological attitude and improve their compliance with relevant EBP steps. In the study of Meng *et al*[28], the application of an EBP project based on MDT to postpartum anxiety and depression also significantly reduced adverse mood and improved patients' nursing satisfaction, which supports our findings. Another study pointed out that the EBP project based on MDT can assist patients undergoing gynecological laparoscopic surgery with propofol and fentanyl to improve their mental health, similar to our research results[29]. Dai *et al*[30] also reported that evidence-based nursing interventions based on MDTs are beneficial for improving the cognitive function of patients in intensive care units, which is mainly reflected in significantly increased Mini-Mental State Examination scores and a reduced incidence of delirium after intervention, which is consistent with our research results. In this study, the improvement in cognitive function in gynecological perioperative patients by the MDT-based EBP project may be related to its effective reduction in the incidence of hypothermia.

MDTs facilitate the effective management of PH in gynecological patients

Munday *et al*[7] reported that intervention strategies based on the MDT model can maximize the effect of PH prevention and management. Drawing on the i-PARIHS framework, this study found that communication was blocked in the prevention and management of PH in gynecological patients among nurses from different departments. At present, there is a fault segmentation in the temperature management of patients in the operating room, gynecological ward and PACU, and patient transport and handover are neglected. To solve this obstacle, the EBP project established a multidisciplinary collaboration team led by nurses, clarified the division of team roles, detailed the professional responsibilities of the preoperative ward, preoperative preparation room, intraoperative operating room, postoperative PACU, and postoperative 24-hour gynecological ward in the prevention and management of hypothermia throughout the perioperative period of gynecological patients, and set up a WeChat communication group to ensure smooth and timely response of information among disciplines, thus promoting communication and cooperation among multiple disciplines, which was consistent with the research results of Shi *et al*[31]. In addition, the body temperature supervision mechanism and the overall quality control process led by the head nurses of the operating room, gynecology and anesthesiology departments were improved. Furthermore, the head nurses reported the practice changes to the evidence-based team monthly to allow for time identification of barriers and facilitators. Moreover, the evidence-based team conducted a quality inspection every quarter to solve problems such as nurses' inadequate assessment of hypothermia risk factors, insufficient supply of 38-40 °C irrigation solution during operations, and inadequate adjustment of ambient temperature to ensure reasonable, feasible and perfect implementation of all aspects and further promote the effective management of PH in gynecological patients. MDTs can integrate medical resources and lead patients to better rehabilitation outcomes [32].

The MDT-based EBP project needs further continuous improvement

The KTA model emphasizes the continuous use and consolidation of knowledge[8], that is, continuous quality improvement of the project after implementation and evaluation. The commonly used quality improvement models are PDCA circulation and quality control circles, which have been widely applied in medical and nursing fields and have achieved remarkable results in advocating medical and nursing quality improvement. In this study, the implementation rate of intraoperative temperature monitoring equipment use and intraoperative temperature monitoring every 15 min in gynecological surgery patients was 66.67% after the application of the EBP project, indicating the poor implementation of intraoperative body temperature monitoring and the need for further improvement. This is related to the use of wireless temperature monitoring equipment in the pilot operating room. This device can realize continuous monitoring of core temperature every minute, but there are some problems, such as a high cost of use, discontinuous temperature monitoring due to a weak Bluetooth signal during operations, and equipment failure, which makes some patients refuse to use temperature monitoring equipment, resulting in loss of temperature monitoring values. Patients who refuse to use wireless temperature monitoring equipment have to be monitored manually by visiting nurses every 15 min, which increases the nurses' workload and leads to the low implementation rate of nurses' norms. On the other hand, in this EBP project, although body temperature management of patients in the PACU was strengthened, there was a lack of thermal insulation equipment for patients with hypothermia. Studies have shown that using the modified inflatable thermal insulation quilt for patients with mild hypothermia has the same warming effect as the inflatable heating blanket, which can not only reduce costs but also be suitable for rewarming PACU patients with hypothermia. Therefore, the common quality improvement model can be combined in the future to further optimize PH prevention and management in gynecological patients.

CONCLUSION

This study focused on the high incidence of PH in gynecology. Guided by KT drawing on the best evidence and i-PARIHS framework and combined with the wishes of stakeholders and expert opinions, an EBP project based on an MDT was formulated and implemented, which effectively promoted the application of evidence, strengthened multidisciplinary cooperation, standardized the prevention and management of PH in gynecology, improved nurses' awareness, and effectively enhanced nursing quality. For gynecological patients during the perioperative period, this project lowered the incidence of PH and improved their thermal comfort level, psychological status and cognitive function. However, the implementation effect of some examination indicators was still not satisfactory, and relevant procedures and systems need further optimization. In the future, how to standardize the monitoring of patients' continuous body temperature during surgery needs further discussion.

ARTICLE HIGHLIGHTS

Research background

Perioperative hypothermia (PH) has varying degrees of negative effects on the physical and mental health of patients, and there is no effective multidisciplinary team (MDT) intervention for PH in gynecological patients.

Research motivation

Despite the comprehensiveness and maturity of the practice guidelines and evidence summaries on PH prevention and management in foreign countries, there is a lack of effective clinical practice for PH in gynecological patients in China, so it is necessary to conduct this analysis to fill in this gap.

Research objectives

To apply the best evidence on the prevention and management of PH in gynecological patients, to improve the quality of perioperative evidence-based care based on MDT treatment of gynecological patients, and to analyze the effect of MDT-based evidence-based practice (EBP) project on the psychological status and cognitive function of gynecological patients with PH.

Research methods

Under the guidance of knowledge translation and combined with the opinions of stakeholders involved and clinical experts, the best evidence for PH prevention and management in gynecological patients was selected and adjusted to suit the practice setting. Based on the evidence, the practice plan was developed, and the MDT intervention was carried out in the preoperative ward, the preoperative preparation room, the intraoperative operating room, the postanesthesia care unit, and the 24-hour postoperative gynecological ward through the EBP program. The incidence of hypothermia, the nurses' awareness, the implementation rate of examination indicators, and the thermal comfort level, psychological status and cognitive function of patients were compared before and after the program application.

Research results

The incidence of PH in gynecological patients decreased from 43.33% to 13.33% after the application of the scheme. The implementation rate of examination indicators 6-10, 12, 14, 16-18, 21, and 22 reached 100%, and that of other indicators was above 90% except for examination indicators 5 and 13, which was 66.67%; the indexes were significantly improved compared with the baseline (before evidence application), with statistically significance ($P < 0.05$). The score of nurses' awareness of PH prevention and management in gynecological patients increased from (60.96 ± 9.70) to (88.08 ± 8.96), and the difference was statistically significant ($P < 0.001$). The total score of perioperative thermal comfort level of patients undergoing gynecological surgery was (27.97 ± 2.04), which was statistically increased compared with the score of (21.27 ± 1.57) investigated by researchers at baseline ($P < 0.001$). The perioperative Hamilton Anxiety Scale and Hamilton Depression Scale scores of patients undergoing gynecological surgery decreased from (15.03 ± 3.16) and (13.93 ± 2.64) to (4.30 ± 1.15) and (3.53 ± 0.78), respectively, with statistically significant differences ($P < 0.001$). The perioperative Montreal Cognitive Assessment Scale score of the gynecological surgery patients increased from (23.17 ± 1.68) to (26.93 ± 1.11), also with statistical significance.

Research conclusions

MDT-based EBP of PH prevention and management in gynecological patients during the perioperative period can standardize nursing operations, improve nurses' awareness and behavioral compliance with gynecological hypothermia management, and reduce the occurrence of PH in gynecological patients, while playing a positive role in reducing patients' negative emotions and enhancing their cognitive function.

Research perspectives

MDT-based EBP has certain effectiveness in perioperative PH prevention and management of gynecological patients and can improve patients' psychological state and cognitive function. However, it is still necessary to solve the problem that the accuracy rate of intraoperative temperature monitoring is less than 80%.

FOOTNOTES

Author contributions: Liu QY designed the study; Liu QY, You TY, Zhang DY and Wang J performed the data collection and conducted the data analysis; Liu QY wrote the manuscript; Liu QY and Wang J revised the manuscript; all authors approved the final version of the manuscript.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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ORIGINAL ARTICLE

Retrospective Study

Effect of Internet + continuous midwifery service model on psychological mood and pregnancy outcomes for women with high-risk pregnancies

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Abstract

BACKGROUND

There are many drawbacks to the traditional midwifery service management model, which can no longer meet the needs of the new era. The Internet + continuous midwifery service management model extends maternal management from prenatal to postpartum, in-hospital to out-of-hospital, and offline to online, thereby improving maternal and infant outcomes. Applying the Internet + continuous midwifery service management model to manage women with high-risk pregnancies (HRP) can improve their psycho-emotional opinion and, in turn, minimize the risk of adverse maternal and/or fetal outcomes.

AIM

To explore the effectiveness of a midwife-led Internet + continuous midwifery service model for women with HRP.

METHODS

We retrospectively analyzed the clinical data of 439 women with HRP who underwent prenatal examination and delivered at Shanghai Sixth People's Hospital (affiliated to the Shanghai Jiao Tong University School of Medicine) from April to December 2022. Among them, 239 pregnant women underwent routine obstetric management, and 200 pregnant women underwent Internet + continuous midwifery service mode management. We used the State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale, and analysis of delivery outcomes to compare psychological mood and the incidence of adverse delivery outcomes between the two groups.

RESULTS

The data showed that in early pregnancy, the anxiety and depression levels of the two groups were similar; the levels gradually decreased as pregnancy progressed, and the decrease in the continuous group was more significant [31.00 (29.00, 34.00) *vs* 34.00 (32.00, 37.00), 8.00 (6.00, 9.00) *vs* 12.00 (10.00, 13.00), $P < 0.05$]. The maternal self-efficacy level and strategy for weight gain management were better in the continuous group than in the traditional group, and the effective rate of midwifery service intervention in the continuous group was significantly higher than in the control group [267.50 (242.25, 284.75) *vs* 256.00 (233.00, 278.00), 74.00 (69.00, 78.00) *vs* 71.00 (63.00, 78.00), $P < 0.05$]. The incidence of adverse delivery outcomes in pregnant women and newborns and fear of maternal childbirth were lower in the continuous group than in the traditional group, and nursing satisfaction was higher [10.50% *vs* 18.83%, 8.50% *vs* 15.90%, 24.00% *vs* 42.68%, 89.50% *vs* 76.15%, $P < 0.05$].

CONCLUSION

The Internet + continuous midwifery service model promotes innovation through integration and is of great significance for improving and promoting maternal and child health in HRP.

Key Words: Internet + continuous midwifery service; High-risk-pregnancy management; Psychological mood; Pregnancy outcome; Traditional midwifery service model; Midwife

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Core Tip: The Internet + continuous midwifery service model promotes innovation through integration, breaks the limitations of time and space in the traditional midwifery service supply mode, and enables pregnant women to enjoy high-quality nursing services at home. However, it is necessary to determine the feasibility and effectiveness of the midwife-led Internet + continuous midwifery service model, especially in women with high-risk pregnancies (HRP). By retrospectively analyzing the clinical data of 439 women with HRP, we clarified the positive effect of the midwife-led Internet + continuous midwifery service model on the psychological mood and pregnancy outcomes of women with HRP.

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INTRODUCTION

High-risk pregnancies (HRP) are those with a high probability of dystocia, endangering the safety of the parturient and child. Data show that women with HRP in foreign countries account for 6% to 33% of all pregnant women[1], while the incidence of HRP in China is as high as 30%, which means that nearly one-third of pregnant women face adverse pregnancy outcomes such as dystocia, intrauterine death, postpartum hemorrhage, and puerperal infection. The National Institute for Health and Care Excellence (NICE) guidelines[2] indicate that effective communication, timely care, and treatment in early pregnancy, as well as professional care during and after delivery, can minimize the risk of adverse maternal and/or fetal outcomes.

In recent years, after a long period of practical exploration and theoretical research, domestic experts have achieved fruitful results in Internet + continuous midwifery service models. This service model overcomes the limitations of time and space of midwifery services, combines the advantages of the Internet, and gives full play to the subjective initiative of midwifery personnel. It can fully grasp the dynamic changes in parturients and newborns before, during, and after delivery and realize the long-term, continuous, and real-time management of pregnant and lying-in women by combining online and offline methods[3,4]. A systematic review pointed out that this nursing model enables pregnant women and midwives to establish partnerships during the prenatal, childbirth, and postpartum stages. Compared to other nursing models, it can reduce the necessity for maternal and infant treatment interventions[5]. Due to the gradual implementation of the Internet + continuous midwifery service model in maternal healthcare, a number of women with HRP were helped by the Internet + continuous midwifery service model between 2021 and 2022. However, it is necessary to determine the feasibility and effectiveness of the midwife-led Internet + continuous midwifery service model, especially the psychological emotions and pregnancy outcomes of women with HRP. This study retrospectively analyzed the role of the Internet + continuous midwifery service model for women with HRP.

MATERIALS AND METHODS

Patient characteristics

First, this was a retrospective study. Clinical data of 439 women with HRP, who underwent prenatal examination and delivered at Shanghai Sixth People's Hospital affiliated to the Shanghai Jiao Tong University School of Medicine from April 2022 to December 2022, were analyzed. According to the different midwifery service modes, participants were divided into a traditional group (TG, n = 239) and a continuous group (CG, n = 200). Inclusion criteria: (1) Age ≥ 18 years; (2) women with HRP with pregnancy risk assessment grade of "orange," "red," or "purple" in the "Maternal Pregnancy Risk Assessment and Management Standards" issued by the National Health and Family Planning Commission of the People's Republic of China; (3) women with HRP who can skillfully use an Internet smartphone; and (4) women with HRP who signed informed consent forms. Women with HRP with mental illness, who could not communicate, or lacked research data were excluded.

TG

The TG adopted a routine obstetric management mode; that is, the prenatal and postpartum stages were mainly managed by doctors, and midwives participated in the entire process of maternal production. During the prenatal checkup phase, obstetricians perform routine examinations and provide health education to pregnant women. In the waiting room, midwives provide prenatal care to pregnant women experiencing pain. In the delivery room, midwives assist parturients with delivery, perform lateral incisions, correctly assess fetal conditions, and provide basic care. An obstetric nurse is responsible for nursing management in the postpartum stage, such as health education, diet guidance, and puerperal care. On the day of discharge, the obstetric nurse provides health education to the parturient and instructs her to attend the obstetric clinic for review and health guidance 42 d after delivery.

CG

The CG implemented an Internet + continuous midwifery service model based on a traditional group, which was completed in three steps.

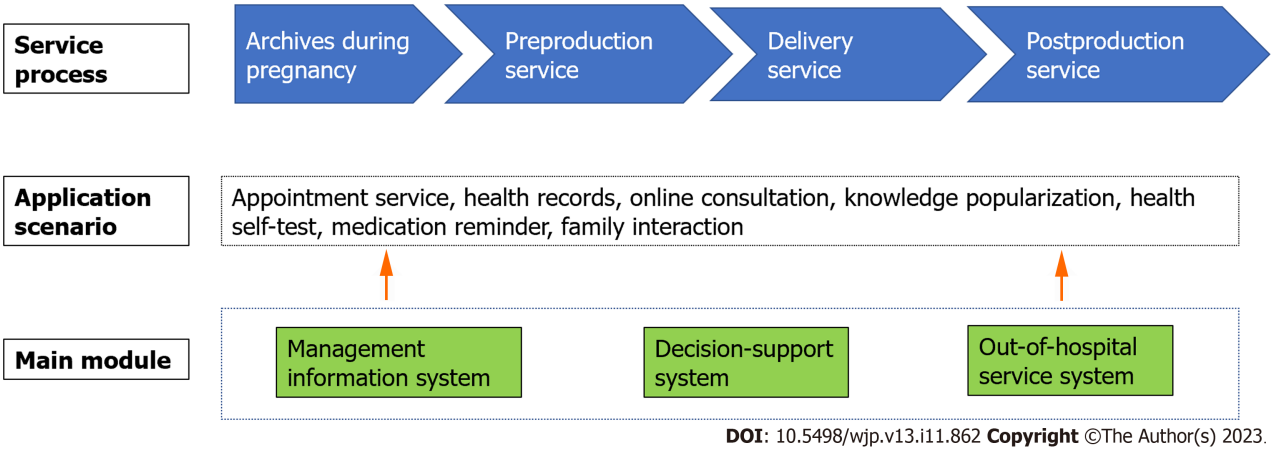
Step 1: Conduct expert meetings and establish a continuous midwifery service management team. Experts in related fields set up an expert group to put forward opinions and suggestions on the process and connotations of the Internet + continuous midwifery service mode. We have revised and improved these details. The continuous midwifery service management team comprised eight midwifery specialist nurses, three maternal and infant specialist nurses, and two neonatal specialist nurses. The head nurse of the department served as the group leader and was responsible for providing suggestions and opinions on the processes and connotations of continuous midwifery services. As the deputy leader, the head nurse was responsible for leading the team members to construct the initial implementation plan and organizing the members to carry out relevant training and assessment. In addition to participating in the above work, the remaining team members needed to implement Internet + continuous midwifery services for pregnant women.

Step 2: Establish an HRP Maternal Internet Communication Platform. During the recruitment of pregnant women participants, midwives invited them to join an Internet communication WeChat group and introduced WeChat group functions such as viewing popular science articles, downloading educational videos at different stages, and making group videos or voice calls. At the same time, team members were responsible for the implementation of WeChat group online interactions, irregularly and dynamically carrying out relevant health knowledge education for pregnant women and their families, and encouraging pregnant women to share their experiences and exchange experiences to indirectly alleviate maternal fear, anxiety, and other adverse psychological emotions. In addition, the midwives used videoconferencing software to regularly conduct pregnancy care courses and answer questions online. At the same time, the questionnaire star is used to collect relevant data.

Step 3: Carrying out Internet and continuous midwifery services. The midwife-led Internet + continuous midwifery service is divided into three periods: Prenatal stage [(1) first trimester < 14 wk; (2) 14-28 wk in the second trimester; and (3) > 28 wk in the third trimester), delivery stage (labor to 2 h after delivery), postpartum stage (4-6 wk after delivery)]. The specific process is shown in Figures 1 and 2.

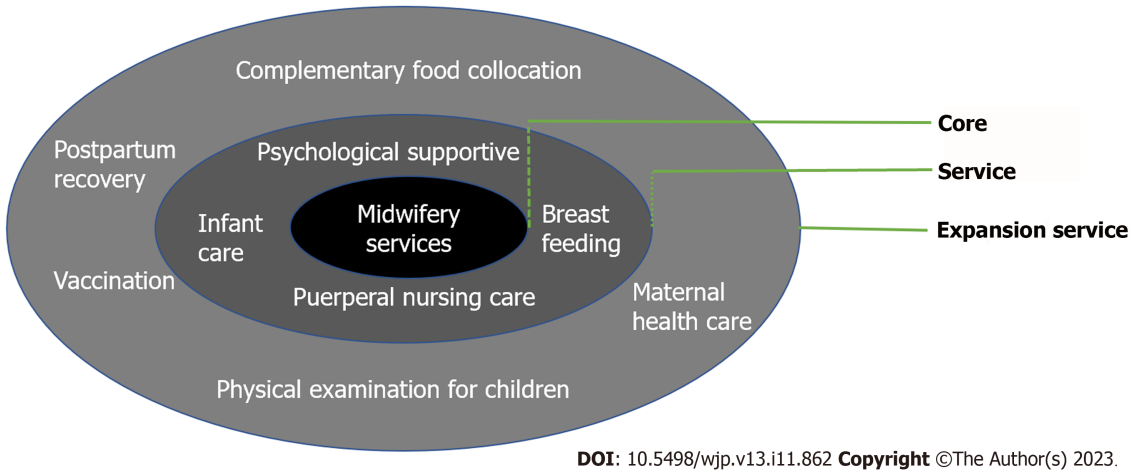
Prenatal stages: Midwives used pregnancy anxiety, fear of childbirth, delivery efficiency, and weight management scales to evaluate the relevant situations of pregnant women. Based on the results of the nutritional analysis and the situation of the pregnant women, a personalized pregnancy management plan was initially formulated. The WeChat group regularly introduced knowledge related to pregnancy care, childbirth, and child-rearing every week through video teaching, text, pictures, and small videos. At this stage, midwives regularly used online video conference calls to communicate with pregnant women one-on-one to understand their needs and conditions. In the third trimester of pregnancy, midwives provided maternal health education related to the delivery stage, including delivery methods, processes, and techniques, and played introductory online videos of maternity wards and delivery rooms to familiarize them with the environment and relieve anxiety.

Delivery stage: During the period from labor to two hours after delivery of the placenta, the team leader selected team members to be responsible for midwifery according to the individual situation of the parturient and provided corresponding nursing services. This included the assessment of maternal and infant conditions, regular monitoring of maternal and fetal conditions, all basic care during labor and delivery, preliminary examination of newborns after delivery, breastfeeding, treatment of the placenta, perineal incision or wound suture, and registration of neonatal birth.



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Figure 1 Application of Internet in continuous midwifery service mode.



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Figure 2 Extension of out-of-hospital midwifery services.

Postpartum stage: Midwives provided postpartum health education for parturients and their families, including wound treatment, postpartum exercise nursing, neonatal feeding knowledge, and nursing. Midwives regularly communicated with parturients on WeChat every week to provide advice on puerperal care, breastfeeding, and maternal and child nutrition.

Effect evaluation

Main outcome measures: (1) Psychological Mood. The State-Trait Anxiety Inventory (STAI)[6] was used to evaluate anxiety. It included a total of 20 items, with a score of 1-4 and a total score of 20-80 points. The higher the score, the more serious the anxiety. The Edinburgh Postnatal Depression Scale (EPDS)[7,8] was used for the psychological assessment of depression, with a total of 10 items, a score of 0-3, and a total score of 0-30. Higher scores indicate more severe depression; and (2) Adverse delivery outcomes. The delivery outcomes of pregnant women and newborns were recorded, including postpartum hemorrhage, postpartum infection, premature rupture of membranes, neonatal asphyxia, fetal distress, fetal weight abnormalities, and premature delivery.

Secondary outcome: (1) Self-efficacy. A simplified Chinese version of the Childbirth Self-Efficacy Scale (CBSEI-C32)[9] was used for the measurements. The total score ranges from 32 to 320 points. Higher scores indicate higher delivery self-efficacy; (2) Childbirth Attitudes Questionnaire (CAQ)[10] was used to assess the fear of childbirth for women in late pregnancy. The total score was 16-64 points, with < 28 points indicating no fear of childbirth, 28-39 points indicating mild fear, 40-51 points indicating moderate fear, and 52-64 points indicating high fear; (3) Weight management. Pregnancy Weight Management Strategy Scale (PWMSS)[11] consists of 18 items, a 1-5 grade score, and a total score of 18-90 points. The higher the score, the more weight gain management strategies were used during pregnancy; and (4) Maternal nursing satisfaction was assessed using a self-administered nursing satisfaction questionnaire.

Statistical analysis

All data were analyzed using SPSS 24.0. Enumeration data were expressed as frequencies and constituent ratios, and

Table 1 Clinical information of women with high-risk pregnancies

Variables	TG (*n* = 239)	CG (*n* = 200)	χ^2/*Z* value	*P* value
Age (yr), IQR	29.00 (27.00, 32.00)	30.00 (26.25, 33.00)	-1.591	0.112
Types of pregnant women, *n* (%)			2.196	0.138
Primipara	49 (20.50)	53 (26.50)		
Pluripara	190 (79.50)	147 (73.50)		
Educational level, *n* (%)			0.415	0.813
Junior high school and below	40 (16.70)	37 (18.50)		
High school or technical secondary school	124 (51.80)	98 (49.00)		
Junior college and above	75 (31.30)	65 (32.50)		
HRP factor, *n* (%)				
Pregnancy complication	87 (36.40)	68 (34.00)	0.275	0.600
Abnormal body mass index	54 (22.50)	33 (16.50)	2.545	0.111
Scarred uterus	41 (17.10)	37 (18.50)	0.135	0.713
Adverse pregnancy	40 (16.70)	31 (15.50)	0.123	0.726
Arrhythmia	39 (16.30)	25 (12.50)	1.275	0.259

Pregnancy complications refer to pregnancy with anemia, diabetes, hypertension, *etc*.; Abnormal body mass index (BMI) refers to a BMI > 25 kg/m^2 or < 18.5 kg/m^2; The same women with high-risk pregnancies can experience two or more risk factors. HRP: High-risk pregnancies; IQR: Interquartile range; TG: Traditional group; CG: Continuous group.

measurement data with a non-normal distribution were expressed as interquartile ranges. Enumeration data were analyzed by χ^2 test, and measurement data were analyzed by a nonparametric Mann-Whitney *U* test. Repeated-measures analysis of variance was used to analyze the results of multiple measurements. The rank-sum test was used for the grade data. $P < 0.05$ was considered as statistically significant.

RESULTS

Clinical characteristics

There was no statistical difference in the general clinical data between the two groups ($P > 0.05$) (Table 1).

Psychological and emotional changes in women with HRP

In the first trimester, the anxiety and depression levels of the two groups were similar and decreased gradually as pregnancy progressed; the CG decreased more significantly ($P < 0.05$) (Table 2).

Self-efficacy changes of women with HRP

There was no statistically significant difference between the two groups in the CBSEI-C32 scores in the first trimester ($P > 0.05$). The CBSEI-C32 scores increased as pregnancy progressed ($P < 0.05$), and the extent of the increase in the CG was greater than that in the TG ($P < 0.05$) (Table 3).

The fear of childbirth in women with HRP in the third trimester of pregnancy

Overall, the effectiveness rate of midwifery interventions in the CG was significantly higher than that in the TG, and the degree of maternal fear of childbirth was lower; the difference was statistically significant ($Z = -4.190$, $P < 0.05$) (Figure 3).

Weight management during pregnancy for women with HRP

In early pregnancy, there was no significant difference in PWMSS scores between the two groups ($P > 0.05$). The PWMSS score increased with an increase of pregnancy ($P < 0.05$). The PWMSS scores of the CG were better than those of the TG ($P < 0.05$) (Table 4).

Adverse birth outcome

In the TG, the incidence of adverse birth outcomes was 18.83% (45/239), and the incidence of adverse neonatal outcomes was 15.90% (38/239). In the CG, the incidence of adverse birth outcomes was 10.50% (21/200), and the incidence of adverse neonatal outcomes was 8.50% (17/200). The CG level was lower than the TG level (all $P < 0.05$) (Table 5).

Table 2 Psychological and emotional changes of women with high-risk pregnancies

Groups		First trimester	Second trimester	Late pregnancy	Postpartum	*F* value	*P* value
Anxiety	TG	65.00 (60.00, 70.00)	57.00 (53.00, 61.00)	40.00 (37.00, 43.00)	34.00 (32.00, 37.00)	215.238	< 0.05
	CG	64.50 (59.00, 68.00)	50.00 (46.00, 54.00)	36.00 (31.25, 40.00)	31.00 (29.00, 34.00)		
	Z value	-1.095	-10.591	-7.703	-7.913		
	P value	0.274	< 0.05	< 0.05	< 0.05		
Depression	TG	22.00 (20.00, 24.00)	19.00 (17.00, 22.00)	19.00 (16.00, 21.00)	12.00 (10.00, 13.00)	196.103	< 0.05
	CG	22.00 (19.00, 24.00)	17.00 (14.25, 19.00)	15.00 (13.00, 17.00)	8.00 (6.00, 9.00)		
	Z value	-0.530	-5.941	-11.048	-12.116		
	P value	0.596	< 0.05	< 0.05	< 0.05		

TG: Traditional group; CG: Continuous group.

Table 3 Changes of self-efficacy in women with high-risk pregnancies

Groups	First trimester	Second trimester	Late pregnancy	Postpartum	*F* value	*P* value
TG	90.00 (83.00, 96.00)	133.00 (123.00, 148.00)	202.00 (187.00, 223.00)	256.00 (233.00, 278.00)	462.402	< 0.05
CG	92.00 (82.00, 97.00)	152.00 (139.00, 165.00)	234.50 (214.25, 257.75)	267.50 (242.25, 284.75)		
Z value	-0.802	-8.374	-9.794	-3.229		
P value	0.423	< 0.05	< 0.05	0.001		

TG: Traditional group; CG: Continuous group.

Table 4 Changes in weight management in women with high-risk pregnancies

Groups	First trimester	Second trimester	Late pregnancy	Postpartum	*F* value	*P* value
TG	33.00 (29.00, 38.00)	42.00 (37.00, 47.00)	68.00 (60.00, 73.00)	71.00 (63.00, 78.00)	30.284	< 0.05
CG	33.00 (28.00, 36.00)	45.00 (40.00, 50.00)	68.00 (64.00, 73.00)	74.00 (69.00, 78.00)		
Z value	-0.743	-3.992	-2.004	-3.059		
P value	0.458	< 0.05	0.045	0.002		

TG: Traditional group; CG: Continuous group.

Table 5 Adverse pregnancy outcomes of parturients and child, *n* (%)

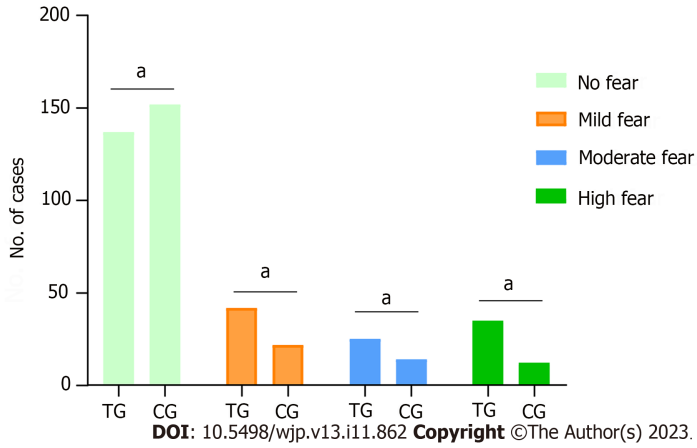
Groups	Parturients				X^2 value	*P* value	Child				X^2 value	*P* value
	Postpartum hemorrhage	Postpartum infection	Premature rupture of membranes	Other			Neonatal asphyxia	Premature delivery	Abnormal fetal weight	Other		
TG	15 (6.28)	9 (3.77)	8 (3.35)	13 (5.44)	5.912	0.015	8 (3.35)	11 (4.60)	7 (2.93)	12 (5.02)	5.44	0.02
CG	7 (3.50)	4 (2.00)	3 (1.50)	7 (3.50)			3 (1.50)	5 (2.50)	2 (1.00)	7 (3.50)		

TG: Traditional group; CG: Continuous group.

Table 6 Nursing satisfaction

Groups	Not satisfied	More satisfactory	Satisfaction	Great satisfaction
TG	59	61	49	70
CG	21	31	55	93
Z value	-5.050			
P value	< 0.05			

TG: Traditional group; CG: Continuous group.



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Figure 3 Fear of childbirth in late pregnancy of two groups of pregnant women. [a]P < 0.05. TG: Traditional group; CG: Continuous group.

Nursing satisfaction

In the CG, nursing satisfaction was 89.50%, which was significantly higher than 76.15% in the TG ($P < 0.05$) (Table 6).

DISCUSSION

The World Health Organization has reported that 50% of maternal deaths and more than 60% of neonatal deaths are caused by poor quality of care. Midwives who have received international standard education can provide women with planned pregnancy guidance and 87% of parturients and child basic care needs, while also avoiding more than 80% of maternal deaths, stillbirths, and neonatal deaths[12]. Among these, the quality of nursing before and after delivery and during puerperium is the focus of promoting maternal health. Prenatal monitoring and postpartum rehabilitation nursing are difficult to perform. It is difficult to fully understand the situation of parturients and newborns by simply relying on community home visits. To meet the nursing needs of women with HRP and compensate for the shortcomings of traditional maternal care services, the Internet + continuous midwifery service model, led by hospital midwives and combined with the advantages of the Internet, provides care to women with HRP and improves adverse pregnancy outcomes.

Regarding the prevalence of anxiety and depression in women with HRP, Dagklis *et al*[13,14] studied the incidence of depression in two HRP inpatient maternal samples (24.3% and 28%, respectively). Goetz *et al*[15] reported significant results. We found a similar trend in this study when compared to recently published inpatient samples. Women with HRP had significantly higher levels of anxiety and depression during early pregnancy. After the intervention of the Internet + continuous midwifery services, the levels of anxiety and depression gradually decreased as pregnancy progressed. As far as we know, the anxiety and depression of women with HRP are caused by many factors. On the one hand, the fear, worry, and pressure of coronavirus disease 2019 may endanger their own and fetal life and health; on the other hand, women with HRP are constrained by time and transportation problems and are unable to perform pregnancy tests on time, thus creating anxiety[16]. From the perspective of the space in which pregnant women receive midwifery services, traditional midwifery services are limited to the management process of pregnant women in hospital, unable to effectively supervise and guide pregnant women outside hospital and predict in advance the risk signals that may trigger HRP or produce adverse pregnancy outcomes. In the Internet + continuous midwifery service dominated by midwives, relying on the WeChat communication group, midwives can provide long-term, continuous, and real-time health counseling for pregnant women, management of normal pregnancy, delivery and puerperium, neonatal care, follow-up postpartum rehabilitation, women's health care, children's physical examinations, and vaccinations[17,18]. In long-term communication, midwives and pregnant women form a stable nurse-patient relationship, reduce the psychological

burden on pregnant women, and alleviate anxiety and depression[19]. Self-efficacy refers to the belief that an individual can perform certain behavioral operations. It plays an important role in controlling or adjusting individual behavior and is related to psychological emotions[20]. Studies have found that the main cause of maternal anxiety is uncertainty in the delivery process and that good self-efficacy can reduce anxiety[21]. The above shows that Internet + continuous midwifery services can effectively improve the psychological mood of women with HRP and improve their self-efficacy.

The self-management ability of pregnant women plays an indispensable role in weight control during pregnancy, especially in compliance and daily life behaviors of pregnant women. Internet + continuous midwifery service completes the monitoring of health indicators independently by adopting online and offline methods, enhancing the sense of self-control of perinatal health care, promoting the formation of good self-management consciousness in pregnant women, and promoting the transformation of health behavior[22]. Ge *et al*[11] found that the self-efficacy of pregnant women can affect their weight management behaviors. Pregnant women can have a high degree of self-evaluation after realizing that they can manage their pregnancy weight well, which promotes weight management behaviors.

Due to the separate nature of previous midwifery services, contact between midwives and pregnant women was limited by time and space, resulting in problems such as a lack of knowledge and fear of childbirth. In CG, mobile Internet technology can effectively meet the diverse needs of pregnant women during pregnancy[23]. Midwives encouraged their families to participate in the learning of knowledge during pregnancy, delivery, and postpartum, and understand the psychological and physiological changes of pregnant women. They can provide pregnant women with more emotional support and positive encouragement during labor, which is conducive to reducing the fear of childbirth and achieving good pregnancy outcomes. This is consistent with the results of a previous study[5]. In addition, midwives work closely with the grassroots medical staff to cooperate and support each other in providing extended midwifery services. When necessary, midwives can use Internet technology to achieve information sharing and two-way referrals.

CONCLUSION

The combination of Internet- and midwife-led continuous midwifery services can effectively expand the use of high-quality nursing service resources, realize the integrated management of women with HRP before and after delivery, and support special groups of women with HRP. Midwives provide effective, economical, and convenient personalized nursing measures for pregnant women during pregnancy, childbirth, and puerperium, which not only reduces the anxiety and depression of women with HRP, but also improves the quality of life of women with HRP and newborns.

ARTICLE HIGHLIGHTS

Research background

There are many drawbacks to the traditional midwifery service management model that can no longer meet the needs of the new era. Dominated by midwives and combined with the advantages of the Internet, continuous midwifery services are provided to women with high-risk pregnancies (HRP) to alleviate adverse psychological emotions and improve pregnancy outcomes.

Research motivation

It is necessary to determine the feasibility and effectiveness of the midwife-led Internet + continuous midwifery service model, especially the psychological emotions and pregnancy outcomes of women with HRP.

Research objectives

To analyze the effect of a midwife-led Internet + continuous midwifery service model on the psychological mood and pregnancy outcomes of women with HRP.

Research methods

The clinical data of 439 women with HRP were retrospectively analyzed. They were divided into different midwifery service modes (traditional and continuous groups). Psychological and emotional conditions, self-efficacy, incidence of adverse delivery outcomes, and nursing satisfaction were compared between the two groups.

Research results

The State-Trait Anxiety Inventory and Edinburgh Postnatal Depression Scale scores of the two groups gradually decreased, with the continuous group decreasing faster than the traditional group. The incidence of adverse delivery and neonatal outcomes in the continuous group was 10.50% (21/200) and 8.50% (17/200), respectively, significantly lower than in the traditional group (18.83%, 45/239; 15.90%, 38/239, respectively).

Research conclusions

The Internet + continuous midwifery service model gives full play to the subjective initiatives of pregnant women and midwives. It is of great significance to realize long-term, continuous, and real-time maternal management and ensure maternal and child safety through "prenatal-intrapartum-postpartum," in-hospital and out-of-hospital, online, and offline

care.

Research perspectives

Midwives carry out corresponding Internet services according to different stages of pregnancy (early, middle, and late pregnancy), including the release of popular science articles on the public account, WeChat group communication, questionnaire star collection of relevant information, and network video conferences answering questions to guide women with HRP to carry out prenatal examinations and self-monitoring. Midwives can not only provide professional advice during pregnancy and childbirth but also provide extended quality nursing services to improve maternal satisfaction.

FOOTNOTES

Author contributions: Han W and Huang CJ contributed to the conceptualization; Han W contributed to the methodology; Huang CJ contributed to the writing; Huang CQ contributed to the data curation and formal analysis.

Institutional review board statement: The study was reviewed and approved by Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

Informed consent statement: As this is a retrospective study, an exemption from informed consent has been applied for.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The data used in this study can be obtained from the corresponding author.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the relationship between blood pressure variability and subtle cognitive decline in older adults

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Abstract

BACKGROUND

Blood pressure variability (BPV) has been shown to be related to mild cognitive impairment and Alzheimer's disease in a number of studies. However, the relationship between BPV and subtle cognitive decline (SCD) has received minimal attention in this field of research to date and has rarely been reported.

AIM

To examine whether SCD is independently associated with changes in BPV in older adults.

METHODS

Participants were selected based on having participated in cognitive function evaluation and ambulatory blood pressure measurement at the Shanghai Sixth People's Hospital Affiliated with Shanghai Jiao Tong University School of Medicine between June 2020 and August 2022. The participants included 182 individuals with SCD as the experimental group and 237 with normal cognitive function as the control group. The basic data, laboratory examinations, scale tests, and ambulatory blood pressure test results of the two groups were analyzed retrospectively, and the relationship between SCD and BPV was subsequently evaluated.

RESULTS

Significant differences were observed between the two groups of participants ($P < 0.05$) in terms of age, education level, prevalence rate of diabetes, fasting blood glucose level, 24-h systolic blood pressure standard deviation and coefficient of

variation, 24-h diastolic blood pressure standard deviation and coefficient of variation. The scale monitoring results showed significant differences in the scores for memory, attention, and visual space between the experimental and control groups. Logistic regression analysis indicated that age, education level, blood sugar level, and BPV were factors influencing cognitive decline. Linear regression analysis showed that there was an independent correlation between blood pressure variation and SCD, even after adjusting for related factors. Each of the above differences was still significant.

CONCLUSION
This study suggests that increased BPV is associated with SCD.

Key Words: Blood pressure; Variability; Elderly; Subtle cognitive decline relationship

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Core Tip: Cognitive dysfunction is a disease that seriously endangers human health, and its current treatment measures are far from perfect. Early identification, which can facilitate the implementation of early treatment, is the primary focus of this research. Our aim was to explore the correlation between blood pressure variability (BPV) and subtle cognitive decline and to understand whether BPV can be used for early detection of cognitive impairment.

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INTRODUCTION

Alzheimer's disease (AD) is a highly harmful disease. Epidemiological surveys have shown that there are more than 30 million AD patients globally, and it is expected that in 30 years, this number will have expanded to 130 million. Cognitive impairment resulting from AD is serious and irreversible, carries a high disability rate, and is difficult to cure, placing a huge burden on both families and society as a whole[1,2]. Although much work has already been performed in this area, there remains no truly effective therapy for AD. Early identification, screening, detection, and intervention are important for preventing the progression of the disease[3-6]. The National Institute on Aging and the Alzheimer's Association have classified AD into three distinct stages[7]: The AD preclinical stage [subjective cognitive decline and subtle cognitive decline (SCD), AD-derived mild cognitive impairment (MCI), and the dementia stage]. SCD refers to the initial phase of cognitive decline. Memory loss is the primary symptom of AD during this period, although a routine examination cannot indicate MCI caused by dementia. According to prior research, early identification and prompt intervention can help prevent 30% of the risk factors associated with AD[4,8,9]. Therefore, SCD has become a popular topic in early-stage AD research. Unlike gene testing, cerebrospinal fluid, and positron emission tomography (PET), blood pressure variability (BPV) testing is inexpensive, non-invasive, and easy for patients to accept. Determining the correlation between BPV and cognitive impairment can provide valuable insight for clinicians regarding the process of diagnosis and treatment.

BPV, also known as blood pressure volatility, indicates the degree to which an individual's blood pressure fluctuates during a certain period of time and does not depend on blood pressure levels[10-12]. BPV is an indicator of spontaneous fluctuations in blood pressure, which are closely related to arterial remodeling, left ventricular hypertrophy, stroke, and hypertensive renal damage. In the physiological process that emerges during the progression from hypertension to cardio-cerebrovascular events, BPV plays an adverse role at every stage[13-16]. Blood pressure changes that occur within 24 h (short-term BPV) are more valuable for predicting the risk of cardiovascular death than clinical blood pressure. Previously published articles have found that the predictive effect of clinical blood pressure is limited, and short-term BPV can serve as a more accurate indicator than clinical blood pressure; therefore, the use of ambulatory blood pressure monitoring (ABPM) should be widely promoted over the use of clinical blood pressure[17-19]. Previous studies have shown that that BPV is associated with MCI and AD[20-22], but studies on BPV and SCD to date have proven rare. SCD is an early stage of AD, and those with SCD face a significantly higher risk of developing MCI and AD people with SCD than those with normal cognitive function[23-25]. Our aim was to evaluate the correlation between BPV and SCD and to analyze whether BPV could be used as a screening index for early cognitive decline.

MATERIALS AND METHODS

Participants

From June 2020 to August 2022, 1095 people who participated in a routine physical examination at the Department of

Geriatrics of Shanghai Sixth People's Hospital completed the neuropsychological scale test and 24-h ABPM. According to the test results, 237 individuals had normal cognitive function and were classified as the control group (NC), and 182 had SCD and were classified as the experimental group (SCD). The basic data, laboratory examinations, scale tests, and ABPM test results of the SCD and NC groups were retrospectively analyzed, and the relationship between BPV and SCD was subsequently assessed.

Inclusion criteria: (1) Participants aged 60 or older; (2) those who have a primary school level education or higher; and (3) those who possess a normal level of hearing and eyesight.

Exclusion criteria: (1) Patients with MCI and AD; (2) those with a history of cerebrovascular disease, such as brain trauma, cerebral infarction, cerebral hemorrhage, Parkinson's disease, brain tumor, epileptic psychosis, or dysplasia; (3) those with a Hamilton Depression Rating Scale 17-item score of more than 12; (4) those with other diseases affecting cognitive function, such as B12 deficiency, alcoholism, folic acid, drug abuse, syphilis, and AIDS; (5) those with visual impairment, hearing impairment, and limb dysfunction resulting in an inability to complete the neuropsychological scale; and (6) those with serious diseases in major organs, such as the liver, kidneys, heart, and lungs.

Clinical-demographic data

Participants' sex, age, height, weight, educational attainment, and history of chronic diseases were recorded. On the same day, routine blood tests, blood lipids, liver and kidney function, and blood glucose were checked, and a head magnetic resonance imaging examination was conducted.

Cognitive function

In a specialized neuropsychological room, the scale was assessed by trained professionals. Scale detection participants did not participate in the judgment of cognitive diagnosis. Each participant was screened using strict scale tests to assess memory, space, attention, language, execution, and social cognition; the scales utilized included a mini-mental state examination (MMSE), the Chinese version of the Montreal Cognitive Assessment (MoCA; MoCA-CV), Hamilton Depression Scale, Auditory Verbal Learning Test (AVLT), Animal Verbal Fluency Test (AFT), Boston Naming Test (BNT), Symbol Digit Modalities Test (SDMT), Rey-Osterrieth Complex Figure Test (CFT), Trail Making Test Part A (TMT-A) and part B (TMT-B), Prospective Memory Test (PrM), Functional Activities Questionnaire (FAQ), and so on.

ABPM and BPV indices

Twenty-four-hour ABPM: The testing period was from 7:00 on day one to 7:00 the following day, from 7:00 to 21:59 during the day, and was recorded every 30 minutes. At nighttime, the testing period was from 22:00 to 6:59 on the second day, with tests taken every 60 min. To be included in the group, the valid readings had to be greater than 90%. BPV indices included 24-h systolic blood pressure standard deviation (SBP SD) and coefficient of variation (SBP CV) as well as 24-h diastolic blood pressure standard deviation (DBP SD) and coefficient of variation (DBP CV). The coefficient of variation was calculated using the formula CV = 100 × SD/mean.

Biochemical indicators

On the day of the scale test, after fasting for 8 h, venous blood samples were taken and immediately tested for blood glucose (fasting and two hours postprandial blood glucose), blood lipids, serum creatinine, serum uric acid, and so on.

Diagnostic criteria of SCD

A total of six neuropsychological scores were examined using the method by Jak and Bondi: the AFT and a 30-item BNT were administered to evaluate language; the TMT-A and TMT-B were administered to evaluate attention/executive function; and two scales were applied to evaluate memory function - the Rey AVLT, a 30-min delayed free recall test, and AVLT recognition. The criteria were used to determine whether participants had SCD: (1) Cognitive decline on two of the six neuropsychological measures in different cognitive fields, defined as > 1 SD below the age-corrected normative mean; and (2) a FAQ score of 6-8[23].

Statistical analysis

The statistical analysis was conducted using SPSS 24.0. We used the mean ± SD to represent the measurement data, and a *t*-test was applied to compare the NC and SCD groups. A χ^2 test was utilized to compare the counting data between the two groups. A binary logistic regression was used to analyze the related factors of cognitive impairment, and a multiple linear regression was performed to determine cognitive domain scores were correlated with BPV. The level of significance was set at $P \leq 0.05$.

RESULTS

Demographic characteristics of the subjects

Table 1 presents the general characteristics of the participating researchers. Significant differences were observed in age, education level, incidence of diabetes, fasting blood glucose levels, SBP SD, SBP CV, DBP SD, and DBP CV between the NC ang SCD groups. No significant differences in other indices were observed.

Table 1 General characteristics of participants

	NC (*n* = 237)	SCD (*n* = 182)	*P* value
Age, yr	70.35 ± 9.57	72.19 ± 10.31	0.002
Sex (male, %)	169 (71.31%)	127 (69.78%)	0.219
Education, yr	11.49 ± 4.12	10.05 ± 3.79	0.037
BMI (kg/m^2)	22.47 ± 4.91	23.16 ± 5.03	0.291
Smoking, *n* (%)	51 (21.52)	39 (21.43)	0.479
Drinking, *n* (%)	72 (30.38)	57 (31.32)	0.517
Hypertension, *n* (%)	104 (43.88)	83 (45.60)	0.153
Diabetes, *n* (%)	35 (14.77)	31 (17.03)	0.021
CAD, *n* (%)	29 (12.24)	27 (14.84)	0.149
FBG (mmol/L)	5.41 ± 1.17	5.93 ± 1.61	0.037
PBG (mmol/L)	8.75 ± 2.81	8.59 ± 2.63	0.275
Scr (μmol/L)	82.45 ± 29.51	79.43 ± 28.72	0.117
TC (mmol/L)	4.53 ± 1.37	4.19 ± 0.95	0.093
TG (mmol/L)	1.32 ± 0.75	1.42 ± 0.81	0.055
HDL-C (mmol/L)	1.15 ± 0.51	1.17 ± 0.49	0.213
LDL-C (mmol/L)	2.39 ± 0.83	2.21 ± 0.79	0.314
SBP SD	10.52 ± 2.94	14.15 ± 4.37	0.000
DBP SD	7.32 ± 2.74	9.45 ± 3.07	0.040
SBP CV	12.35 ± 3.74	16.97 ± 4.91	0.000
DBP CV	9.85 ± 2.73	12.63 ± 3.81	0.006

NC: The control group; SCD: Subtle cognitive decline; BMI: Body mass index; CAD: Coronary artery disease; FBG: Fasting blood glucose; PBG: Postprandial blood glucose; Scr: Serum creatinine; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; SBP SD: 24-h systolic blood pressure standard deviation; SBP CV: 24-h systolic blood pressure coefficient of variation; DBP SD: 24-h diastolic blood pressure standard deviation; DBP CV: 24-h diastolic blood pressure variation coefficient.

Cognitive scale score

As shown in Table 2, a significant difference was observed between the two groups on the MMSE and the MoCA. A comparison of the scores for each cognitive domain revealed significant differences in attention, memory, and visual space between the two groups.

Analysis of influencing factors of cognitive impairment

Using cognitive decline as a dependent variable and other influencing factors as independent variables, multivariate logistic regression analysis revealed that cognitive decline was significantly correlated with age, education level, diabetes, SBP SD, DBP SD, SBP CV, and DBP CV (Table 3).

Effect of blood pressure variation on cognitive performance

Multiple linear regression analysis demonstrated that memory, attention, and visual-spatial dysfunction in the SCD group were significantly correlated with SBP SD and CV, while DBP SD and CV were significantly correlated with memory impairment. Even adjusting for age, sex, drinking, smoking, education level, body mass index, blood glucose, and blood lipid levels, these differences remained significant (Table 4).

DISCUSSION

This study aimed to identify a simple method for detecting cognitive decline in its early stages. In this retrospective study, BPV was observed to be independently associated with SCD and increased BPV in individuals aged 60 or above and may be seen as a risk factor for SCD.

Current reports on the correlation between BPV and cognitive impairment are inconsistent. Most researchers believe that cognitive impairment is associated with increased BPV. However, different views have been expressed on this topic,

Table 2 Scores of personnel cognition scale in two groups

Index	NC (*n* = 207)	SCD (*n* = 175)	*F* (*P* value)
MMSE	28.97 ± 2.13	26.15 ± 1.62	49.327 (< 0.001)
MoCA	25.74 ± 2.96	22.93 ± 3.27	57.319 (< 0.001)
AVLT recognition	21.39 ± 5.27	19.31 ± 3.77	3.572 (0.041)
AVLT delayed recall	6.32 ± 2.29	4.17 ± 1.59	8.351 (0.011)
BNT	24.15 ± 3.14	22.59 ± 3.57	0.275 (0.179)
SDMT	39.29 ± 12.57	34.26 ± 11.09	4.529 (0.032)
TMT-A	53.14 ± 23.95	57. 83 ± 26.71	0.127 (0.359)
TMT-B	133.49 ± 39.72	154.97 ± 45.21	5.273 (0.019)
Rey CFT copy	34.59 ± 3.71	31.49 ± 4.25	8.319 (0.014)
Rey CFT recall	16.72 ± 5.93	13.27 ± 6.41	9.592 (< 0.001)
AFT	16.79 ± 4.52	16.32 ± 4.17	0.035 (2.531)
PrM	14.31 ± 4.15	12.29 ± 4.52	3.572 (0.031)

NC: The control group; SCD: Subtle cognitive decline; MMSE: Mini-mental State Examination; MoCA: Montreal Cognitive Assessment; AVLT: Auditory Verbal Learning Test; BNT: Boston Naming Test; SDMT: Symbol Digit Modalities Test; TMTA, TMT-B: Trail Making Test Part A and B; Rey CFT: Rey-Osterrieth Complex Figure Text; AFT: Animal Fluency Test; PrM: Prospective Memory Test.

Table 3 Logistic regression analysis influencing factors of cognitive impairment

Index	β	SE	Wald	*P* value	OR	95%CI
Age	0.37	0.09	17.59	0.000	1.63	1.45-1.81
Education	0.75	0.13	20.31	0.000	1.92	1.75-2.31
Diabetes	0.11	0.03	13.27	0.000	1.21	1.09-1.37
SBP SD	1.31	0.24	26.15	0.000	3.95	2.57-4.72
SBP CV	0.95	0.21	30.63	0.000	3.71	2.69-4.63
DBP SD	2.47	0.61	8.59	0.023	9.72	3.51-18.95
DBP CV	0.85	0.19	27.33	0.002	3.01	2.65-3.91

SBP SD: 24-h systolic blood pressure standard deviation; SBP CV: 24-h systolic blood pressure coefficient of variation; DBP SD: 24-h diastolic blood pressure standard deviation; DBP CV: 24-h diastolic blood pressure coefficient of variation.

such as that higher BPV has nothing to do with dementia[26-28]; that patients with increased BPV have higher cognitive scores; and that only the increase in systolic blood pressure variation is related to cognitive decline, while the increase in diastolic blood pressure variation is not. In addition, there are significant differences in the cognitive assessment tools, BPV calculation method, duration of blood pressure monitoring, study population, and sample size among different studies[29-31]. Thus, standardized methods should be considered to compare and determine the significance of various studies. The results of the 24-h ABPM were used to calculate BPV, which is a more objective form of measurement than clinic blood pressure; the equipment is simple, primary medical institutions can use it, and research participants can easily accept this method.

At present, effective treatment for dementia remains far from perfect, and many people with cognitive impairment seek treatment in community medical institutions. Identifying changeable risk factors is important for preventing dementia in primary healthcare institutions. ABPM to evaluate blood pressure levels and BPV is a simple method for assessing the risk of dementia and evaluating the effectiveness of treatment.

There are several viewpoints on the mechanism underlying cognitive impairment caused by BPV[32-36]: (1) Hemodynamic instability has harmful effects on neurovascular units and results in endothelial injury and vascular smooth muscle dysfunction, leading to accelerated neuronal damage and neuronal loss; (2) arterial remodeling is beneficial to β-amyloid deposition and reactive glial hyperplasia; (3) the fluctuation of arterial blood pressure leads to inconsistent perfusion attacks of tissue hypoxia-ischemia, promoting the activation of microglia and the production of brain amyloid proteins, resulting in neuronal injury and cell death; and (4) oxidative stress and inflammation. There may be direct connections between vascular and metabolic factors and the deposition of β-amyloid proteins in the brain,

Table 4 Correlation between blood pressure variability and cognitive function by multivariate linear regression analysis

Outcome		Unadjusted model	*P* value	Adjusted model 1	*P* value	Adjusted model 2	*P* value
		β (95%CI)		β (95%CI)		β (95%CI)	
Memory	SBP SD	-0.82 (-1.17 to -0.49)	< 0.001	-0.57 (-0.91 to -0.22)	< 0.001	-0.51 (-0.89 to -0.21)	< 0.001
	SBP CV	-0.79 (-1.15 to -0.42)	< 0.001	-0.61 (-0.93 to -0.32)	< 0.001	-0.59 (-0.91 to -0.25)	< 0.001
	DPB SD	-0.31 (-0.56 to -0.07)	< 0.05	-0.29 (-0.51 to -0.08)	0.029	-0.27 (-0.49 to -0.07)	0.035
	DPB CV	-0.27 (-0.55 to 0.01)	0.037	-0.26 (-0.47 to -0.08)	0.041	-0.23 (-0.41 to -0.03)	0.049
Language	SBP SD	0.04 (-0.02 to 0.09)	0.155	0.03 (-0.01 to 0.07)	0.165	0.03 (-0.02 to 0.09)	0.172
	SBP CV	0.04 (-0.01 to 0.11)	0.153	0.03 (-0.01 to 0.09)	0.167	0.03 (-0.02 to -0.10)	0.157
	DPB SD	0.11 (-0.01 to 0.23)	0.241	0.09 (0.02 to 0.19)	0.305	0.09 (0.01 to 0.18)	0.291
	DPB CV	0.08 (-0.02 to 0.17)	0.195	0.07 (-0.01 to 0.15)	0.236	0.07 (-0.02 to 0.16)	0.229
Attention	SBP SD	-0.76 (-1.07 to -0.39)	< 0.001	-0.67 (-1.03 to -0.21)	< 0.001	-0.70 (-1.01 to -0.39)	< 0.001
	SBP CV	-0.69 (-0.95 to -0.27)	< 0.001	-0.61 (-0.93 to -0.25)	< 0.001	-0.59 (-0.87 to -0.31)	< 0.001
	DPB SD	-0.17 (-0.35 to 0.02)	0.09	-0.11 (-0.32 to 0.01)	0.13	-0.12 (-0.31 to 0.02)	0.13
	DPB CV	-0.15 (-0.29 to -0.01)	0.08	-0.09 (-0.03 to 0.02)	0.15	-0.08 (-0.02 to 0.03)	0.17
Visuospatial ability	SBP SD	-0.27 (-0.39 to -0.14)	< 0.01	-0.21 (-0.35 to -0.10)	< 0.01	-0.20 (-0.33 to 0.06)	< 0.01
	SBP CV	-0.31 (-0.42 to -0.21)	< 0.01	-0.27 (-0.39 to -0.14)	< 0.01	-0.22 (-0.40 to -0.05)	< 0.01
	DPB SD	-0.11 (-0.25 to -0.03)	0.147	-0.07 (-0.02 to 0.03)	0.163	-0.06 (-0.02 to 0.01)	0.179
	DPB CV	-0.15 (-0.29 to 0.01)	0.133	-0.08 (-0.19 to 0.02)	0.182	-0.08 (-0.18 to 0.03)	0.195
Executive function	SBP SD	0.16 (0.05 to 0.28)	0.217	0.12 (-0.02 to 0.23)	0.327	0.11 (-0.01 to 0.27)	0.401
	SBP CV	0.15 (0.05 to 0.26)	0.195	0.11 (-0.01 to 0.21)	0.313	0.10 (0.01 to 0.0.21)	0.374
	DPB SD	0.23 (0.09 to 0.39)	0.291	0.19 (0.03 to 0.34)	0.307	0.17 (0.02 to 0.33)	0.351
	DPB CV	0.19 (0.03 to 0.37)	0.277	0.15 (0.04 to 0.27)	0.295	0.15 (0.04 to 0.29)	0.283
Social cognition	SBP SD	-0.06 (-0.10 to 0.02)	0.571	-0.04 (-0.12 to 0.07)	0.653	-0.03 (-0.11 to 0.06)	0.692
	SBP CV	-0.05 (-0.09 to 0.04)	0.612	-0.02 (-0.13 to 0.11)	0.713	0.01 (-0.14 to 0.13)	0.865
	DPB SD	0.17 (0.08 to 0.27)	0.187	0.14 (-0.03 to 0.31)	0.295	0.13 (-0.02 to 0.29)	0.312
	DPB CV	0.16 (0.04 to 0.29)	0.203	0.13 (-0.01 to 0.30)	0.323	0.12 (-0.02 to 0.27)	0.371

Unadjusted model: Random intercept for the study center. Adjusted model 1: Corrected for age, education, and diabetes. Adjusted model 2: Corrected for age, education, diabetes, body mass index, hypertension, coronary artery disease, smoking, drinking, blood lipids, and serum creatinine levels. SBP SD: 24-hsystolic blood pressure standard deviation; SBP CV: 24-h systolic blood pressure coefficient of variation; DBP SD: 24-h diastolic blood pressure standard deviation; DBP CV: 24-h diastolic blood pressure coefficient of variation.

promoting oxidative stress and inflammation as well as neurodegeneration.

The results of this study show that BPV can be used as a tool to screen for early-stage cognitive decline; therefore, it is possible to delay or prevent further cognitive decline by improving BPV. The sample size of future studies should be increased and long-term follow-up assessments should be conducted to identify the correlation between BPV and cognitive impairment, especially in primary medical institutions as BPV can be considered a valuable tool for screening for cognitive decline.

This study had several limitations, including that it was a small cohort study and that participants were not randomly selected, which could potentially have biased the results. Other indicators that could have an impact on the results were not used in this study to measure BPV. Cerebrospinal fluid and PET tests were not performed, and variations in blood pressure and intracranial lesions could not be identified. Follow-up work should be carried out to extend the results of the study and determine whether effective control of BPV can reduce or reverse the decline in cognitive function. Effective control of BPV was not considered in this study.

CONCLUSION

According to this study, an increase in BPV is one of the risk factors for early cognitive decline. BPV was found to be

independently associated with SCD. BPV should be controlled effectively in clinical practice, especially in the treatment of hypertensive patients. The goal is not only to reach a standard blood pressure level but also to steadily reduce blood pressure and control BPV to better protect cognitive function and try to prevent or delay the occurrence of AD.

ARTICLE HIGHLIGHTS

Research background

Cognitive impairment is a highly harmful disease for which there is no perfect treatment. Early detection and treatment are the main focus of related research. Variation in blood pressure has been correlated with cognitive impairment in previous studies; however, few studies have examined subtle cognitive decline.

Research motivation

Our purpose was to analyze the influencing factors for subtle cognitive decline (SCD) and find a simple and effective index through which to assess cognitive decline that can be used to guide clinical work.

Research objectives

The study aimed to determine whether blood pressure variability (BPV) leads to cognitive impairment. The results showed that an increase in BPV is independently related to SCD and that BPV may be used as a tool for evaluating cognitive impairment and the effectiveness of treatment.

Research methods

We used a standard neuropsychological scale to evaluate cognitive function and retrospectively analyzed the correlation between BPV and SCD.

Research results

The results show that increased BPV may be a factor leading to cognitive decline. The results of such studies are rare; however, the sample size is not sufficiently large, and no further research has been carried out to determine whether it can be used as an index to analyze the effectiveness of treatment.

Research conclusions

This study demonstrates that BPV is a clinical indicator of early cognitive decline. In this study, 24-h ambulatory blood pressure monitoring test was used as an index from which to calculate BPV, one that is simple, effective, and can be readily used in primary healthcare institutions.

Research perspectives

Long-term follow-ups should be considered in the future to further the collective comprehension of the correlation between BPV and cognitive decline and the progress of cognitive impairment as well as to estimate the benefits of improving BPV in the treatment of cognitive impairment.

FOOTNOTES

Co-corresponding authors: Hui-Feng Guo and Yi Wu.

Author contributions: HF Guo and Y Wu analyzed the data and wrote the paper; Li J was responsible for execution and data collection; Pan FF was responsible for the study conception and design; the final version of the manuscript has been approved by all authors. Guo HF and Wu Y contributed equally to this work as co-corresponding authors. The reasons for designating them as co-corresponding authors are as follows: Firstly, this manuscript is a collaborative work. The designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. Secondly, Guo HF and Wu Y contributed equally to this work. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. Guo HF is responsible for the overall planning and the organization of clinical data, Wu Y is responsible for the data summary and statistical analysis. In summary, we believe that designating Guo HF and Wu Y as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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Retrospective Study

Independent risk factors for depression in older adult patients receiving peritoneal dialysis for chronic kidney disease

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Abstract

BACKGROUND

According to the trend of global population aging, the proportion of elderly patients with chronic kidney disease (CKD) is expected to increase. However, there are more than 20 million people in China with decompensated kidney function, of which 19.25% are elderly people. Therefore, special attention should be paid to the education years, sleep quality, anxiety status, comorbidities with diabetes, cardiovascular disease (CVD), and anemia as independent risk factors for depression in elderly CKD patients. This study explores the clinical management of elderly CKD patients that should address these risk factors to prevent depression and improve their prognosis.

AIM

To investigate depression risk factors in older patients receiving peritoneal dialysis, aiding future prevention of depression in these patients.

METHODS

This retrospective study included a primary study population of 170 patients with CKD who received peritoneal dialysis from January 2020 to December 2022. We assessed the patients' mental status using the Beck Depression Inventory Score-II (BDI-II), Self-Rating Anxiety Scale (SAS), Anxiety Inventory Score, and the Pittsburgh Sleep Quality Index (PSQI). Logistic regression was employed to identify depression independent risk factors among these patients.

RESULTS

The non-depressed group had a significantly longer education period than the depressed group ($P < 0.05$). The depressed group exhibited significantly higher mental status scores than the non-depressed group ($P < 0.001$). Patients with diabetes mellitus (DM) or CVD had a higher probability of developing depression. Patients with depression had significantly lower hemoglobin and albumin levels than patients without depression ($P < 0.05$). Spearman correlation

analysis of BDI-II scale scores, measuring depression, indicated positive correlations with BDI-II and SAS scores as risk factors for depression in patients with CKD. In contrast, years of education, hemoglobin levels, and peritoneal Kt/V were negatively correlated, serving as protective factors against depression. An analysis of variance for influences with significant differences in the univariate analysis revealed that years of schooling, BDI-II, SAS, PSQI, DM, CVD, and hemoglobin levels independently influenced depression in older patients with CKD.

CONCLUSION

Education, BDI-II, SAS, PSQI, DM, and CVD are independent risk factors for depression in older patients with CKD; therefore, post-treatment psychological monitoring of high-risk patients is crucial to prevent depression.

Key Words: Depression; Chronic kidney disease; Peritoneal dialysis; Older adults; Risk factors for depression; Beck Depression Inventory Score-II

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Core Tip: We identified independent risk factors for depression in older patients with chronic kidney disease receiving peritoneal dialysis, including fewer years of education, higher Beck Depression Inventory Score-II and Self-Rating Anxiety Scale scores, poorer sleep quality, the presence of diabetes mellitus and cardiovascular disease, and lower hemoglobin and albumin levels. Conversely, more years of education, higher hemoglobin levels, and better peritoneal Kt/V ratio were associated with a lower risk of depression. These findings emphasize the importance of considering psychological well-being and addressing potential risk factors in the management of older patients on peritoneal dialysis, particularly in patients at high-risk of depression.

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INTRODUCTION

Chronic kidney disease (CKD), a severe condition, is associated with a group of syndromes and results from progressive kidney structure and function degradation over three months[1]. Patients with CKD exhibit clinical manifestations such as varying urinary protein levels, swelling, hypertension (HTN), and impaired kidney function[2]. Age significantly contributes to CKD, as kidneys decrease in size and lose with age[3]. In China, at least 20 million people have decompensated kidney function[4], with 19.25% being older adults. With global aging, the proportion of older patients with CKD is also likely to increase, necessitating special treatment and prognosis considerations.

Due to kidney shortages, CKD is often managed with renal replacement therapy, mainly hemodialysis and peritoneal dialysis[5]. Peritoneal dialysis utilizes the peritoneum as a semi-permeable membrane to remove dialysis fluid and metabolic waste[6]. Compared with hemodialysis, peritoneal dialysis is less expensive and has a lower ischemic effect on the kidneys, preserving residual function, and is more accessible[7]. However, CKD not only represents a financial burden to the patients but also leads to a rising rate of CKD-associated disabilities, causing patient suffering[8].

With advances in medical technology, the survival rates of patients with CKD is increasing, resulting in a growing population of patients with CKD[9]. Identifying means to improve their quality of life and prognosis has become a critical research focus. The prevalence of depression among patients with CKD is four times higher than that in the general population[10]. Among patients with CKD receiving ambulatory peritoneal dialysis, most often complain of poor sleep quality, moodiness, and lethargy, with a 58.1% prevalence of depression[11]. Despite variations in depression scales, ethnic groups, and geographic regions, various national and international studies have associated CKD-related depression to higher hospitalization rates, cardiovascular events, and suicide and mortality rates[12-14].

Based on the previous findings, this retrospective study explored the independent risk factors for depression in older patients with CKD receiving peritoneal dialysis to provide a scientific basis for reducing depression and improving the prognosis of older patients.

MATERIALS AND METHODS

Study participants and design

We selected 170 patients with CKD who received peritoneal dialysis treatment at the Cangzhou Central Hospital in the Hebei Province from January 2020 to December 2022. The study was approved by the ethics committee of the Cangzhou Central Hospital and all participants signed informed consent. The patient inclusion criteria were: (1) Age > 65 years; (2)

Met the diagnostic criteria for patients with CKD receiving peritoneal dialysis; (3) Ambulatory with unrestricted activity; and (4) No comorbid psychiatric conditions prior to observation and conscious and able to communicate autonomously. Patients were excluded if they had: (1) An emergency cardiovascular event with impaired consciousness; (2) other serious illnesses, such as cancer, myocardial infarction, and cerebrovascular accident (CVA); and (3) depression and anxiety before receiving peritoneal dialysis.

This retrospective study analyzed patients previously treated with peritoneal dialysis, collected their basic information and clinical data, and assessed their mental status using the Beck Depression Inventory Score-II (BDI-II), Self-Rating Anxiety Scale (SAS), Anxiety Inventory Score, and the Pittsburgh Sleep Quality Index (PSQI).

Clinical characteristics

Demographic information and prevalence data were collected from all participants. These data included age, sex, education level, body mass index (BMI), presence of HTN, presence of diabetes mellitus (DM), and history of cardiovascular disease (CVD). CVDs included coronary heart disease, congestive heart failure, myocardial infarction, and a history of CVA.

Laboratory methods

Peritoneal dialysis was continued after the patients were given a night meal. Venous blood was collected from all participants for routine blood tests. Blood tests were conducted using a fully automated chemistry analyzer (indicators included serum sodium, albumin, calcium, phosphate, cholesterol, and hemoglobin). Midmorning urine samples were collected to determine renal function. The total Kt/V and creatinine clearance of the patients' body after peritoneal dialysis were evaluated to determine the effectiveness of dialysis treatment.

Depressive state measurement

The BDI-II, SAS Anxiety Inventory Score, and PSQI scores were used to measure the depression status of the patients.

BDI-II: This scale assesses the degree of depression. It consists of 21 groups of items, with each group having four statements. Each question is scored from 0 to 3. Depression was classified as follows: patients with scores < 13 were considered non-depressed, 14–19 were considered mildly depressed, 20–28 were considered moderately depressed, and 29–63 were considered severely depressed[15].

SAS: This scale assesses the degree of anxiety. The standard SAS score has a cutoff of 50, with 50–59 indicating mild anxiety, 60–69 indicating moderate anxiety, and 70 or more indicating severe anxiety[16].

PSQI: This index is used to assess sleep quality over the last month. The total PSQI score ranges from 0 to 21. A negative correlation was observed between these scores and sleep quality (higher scores indicating poorer sleep quality). A score > 16 indicated poor sleep quality[17].

Statistical analysis

The data were processed using SPSS 26.0, with measurements expressed as the mean ± SD. Analysis of variance (ANOVA) or Student's *t*-test was performed to evaluate statistical significance. The *t*-test for independent samples was performed to compare the data between the two groups, and the chi-square test was performed to compare the count data in terms of composition ratio (%). Correlations were analyzed using the Spearman method, and influencing factors were analyzed using multiple linear regression models, with $P < 0.05$ considered as a statistically significant difference. Spearman's rank correlation was used to analyze the relationship between depression and each parameter, and logistic regression was performed to analyze the factors influencing depression.

RESULTS

Patient baseline characteristics

We collected demographic data and medical histories for analysis (Table 1). Among 170 patients, 59 were assessed as having depression based on the scale and clinical symptoms. Age, BMI, HTN, triglyceride, P, Ca, Na levels, and renal function did not significantly differ between the depressed and non-depressed groups ($P > 0.05$). However, a significant difference was observed in the length of education between the two groups ($P < 0.05$). The depressed group had significantly higher mental state scores compared to the control group ($P < 0.001$). Patients with DM and CVD were more prone to develop depression, and those in the depressed group had significantly lower hemoglobin and albumin levels than patients in the non-depressed group ($P < 0.05$).

Correlation between depression and relevant indicators in peritoneal dialysis patients

The results of the Spearman correlation analysis of BDI-II scale scores measuring depression with each factor revealed that BDI-II and SAS scores were positively correlated as risk factors for depression in patients with CKD. In contrast, years of education, hemoglobin levels, and peritoneal Kt/V were negatively correlated as protective factors against depression (Table 2).

Dichotomous logistic regression analysis of patient depression

ANOVA results revealed that years of schooling, BDI-II, SAS, PSQI, DM, CVD, and hemoglobin levels independently influenced depression in older patients with CKD (see Table 3 for indicator assignments) (Table 4).

Table 1 The baseline characteristics of the study patients

Factors	No-depression (*n* = 59)	Depression (*n* = 111)	*P* value
Age (yr, mean ± SD)	67.23 ± 0.23	68.11 ± 0.36	0.590
Sex (male/female)	78/33	41/18	0.975
BMI (kg/m^2, mean ± SD)	22.10 ± 0.55	20.83 ± 0.40	0.057
Year of education (yr)	8.0 ± 0.50	5.5 ± 0.50	0.021[1]
Mental State Scale scores			
BDI-II	5.72 ± 0.92	18.13 ± 0.21	< 0.001[3]
SAS	44.11 ± 1.02	60.92 ± 2.90	< 0.001[3]
PSQI	3.90 ± 0.67	19.02 ± 0.82	< 0.001[3]
Medical history			
HTN	21(35.59%)	41 (36.94%)	0.056
DM	35(59.32%)	56 (50.45%)	< 0.001[3]
CVD	12(20.33%)	24 (21.62%)	< 0.001[3]
Physical examination			
Albumin (g/L)	37.78 ± 0.41	31.27 ± 0.13	0.002[2]
Hemoglobin (g/L)	121.40 ± 11.90	103.90 ± 13.33	0.031[1]
Triglycerides (mmol/L)	1.98 ± 0.59	1.56 ± 0.46	0.072
P (mmol/L)	1.82 ± 0.35	1.74 ± 0.12	0.197
Ca (mmol/L)	2.34 ± 0.19	2.24 ± 0.26	0.237
Na (mmol/L)	137.25 ± 12.60	135.01 ± 15.06	0.892
Renal function			
Scr (μmol/L)	352.15 ± 15.65	350.21 ± 15.96	0.145
BUA (μmol/L)	369.78 ± 14.69	357.37 ± 14.34	0.774
Residual renal Kt/V	0.28 ± 0.09	0.26 ± 0.07	0.132
Peritoneal Kt/V	1.56 ± 0.10	1.54 ± 0.21	0.521

[1]$P < 0.05$.
[2]$P < 0.01$.
[3]$P < 0.001$.
HTN: Hypertension; DM: Diabetes Mellitus; CVD: Cardiovascular Disease; BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; Scr: Serum creatinine; BUA: Blood uric acid.

DISCUSSION

Because the older adult population comprises an increasing proportion of patients with CKD, improving their quality of life and prognostic outcomes has become a priority for their clinical management. Depression often results in reduced sleep quality and worry in older patients, which can lead to self-harm and, in severe cases, to suicidal behavior. Studies have evidenced that patients with CKD are more prone to depression than patients without CKD, possibly due to prolonged dialysis treatment and physical and psychological stress[18]. In this retrospective study, we analyzed cross-sectional data and the results revealed that indicators such as years of education and sleep quality are independent risk factors for depression in older patients with CKD.

Association between years of schooling and depression

Educational attainment has consistently been considered as a protective factor against depression. Our study reinforces this connection, revealing a significant negative correlation between that years of education and depression scores. Higher education often equates to lower depression rates associated to greater financial stability and access to health knowledge, fostering better acceptance of the patient's condition[19]. Moreover, the alleviating effect of education on depression increases with age[20]. Therefore, the protective effect of education on depression is more likely to be noted in the older adult population.

Table 2 Correlation between depression and relevant indicators in peritoneal dialysis patients

Factors	r_s	*P* value
Year of education	-0.415	< 0.001[3]
BDI-II	0.925	0.015[2]
SAS	0.982	< 0.001[3]
Hemoglobin	-0.332	0.002[2]
Peritoneal Kt/V	-0.456	0.023[1]

[1]*P* < 0.05.
[2]*P* < 0.01.
[3]*P* < 0.001.
BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale.

Table 3 Influencing factor assignments

Factors	Assignment
Years of schooling	> 6 yr = 0, < 6 yr = 1
BDI-II	< 14 score = 0, ≥ 14 score = 1
SAS	< 50 score = 0, ≥ 50 score = 1
PSQI	< 16 score = 0, ≥ 16 score = 1
DM	No = 0, yes = 1
CVD	No = 0, yes = 1
Albumin	≥ 35 = 0, < 35 = 1
Hemoglobin	< 110 = 1, ≥ 110 = 1

BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; DM: Diabetes Mellitus; CVD: Cardiovascular Disease.

Table 4 Dichotomous logistic regression analysis of patient depression

Indices	β	Wald	*P* value	OR	95% CI
Years of schooling	1.519	1.628	0.025[1]	0.971	0.921-0.987
BDI-II	0.116	5.177	< 0.001[3]	0.258	0.215-0.267
SAS	0.059	2.648	< 0.001[3]	1.605	1.420-1.700
PSQI	0.169	11.029	< 0.001[3]	0.157	0.144-0.162
DM	0.126	8.053	< 0.001[3]	1.264	1.201-1.274
CVD	0.236	2.615	0.002[2]	0.584	0.573-0.600
Albumin	-0.300	5.641	0.051	1.177	1.059-1.208
Hemoglobin	-0.321	3.641	< 0.001[3]	1.060	0.998-1.105

[1]*P* < 0.05.
[2]*P* < 0.01.
[3]*P* < 0.001.
BDI-II: Beck Depression Inventory-II; SAS: Self-Rating Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; DM: Diabetes Mellitus; CVD: Cardiovascular Disease.

Studies have suggested that the education might strengthen the resilience of patients with CKD, reducing their susceptibility to depression. Our findings highlight that patients with lower educational levels are more prone to depression. In China, the majority of the older adults has a low education level, with a 13.90% of those aged ≥ 60 years having a high school education or higher as of 2021. This proportion may be even lower among older patients with CKD who have depression[21].

Association of sleep quality and anxiety with depression

Sleep quality and anxiety levels often conform with depression. Studies have reported that people experiencing poor sleep quality and higher anxiety levels are more likely to develop depression. This result is consistent with that of our study[22]. Sleep quality is crucial for health; however, older adults have significantly shorter sleep duration and generally poorer sleep quality than people from other age groups. From a neurobiological perspective, people with insomnia tend to exhibit increased activity in their arousal systems, leading to alterations in corticothalamic neural activity and neurotransmitter release. This includes the production of high levels of adrenocorticotropic hormones and cortisol, factors that increase susceptibility to mental health conditions such as depression and anxiety[23]. Sleep quality influences cognitive function as well as anxiety and depression in older adults. For example, Wang *et al*[24] found a significant association between sleep disturbance and depression scale and geriatric anxiety scale scores in Asian older adults. Therefore, monitoring sleep quality is crucial for the effective management of older patients with CKD.

Association of DM and CVD with depression

A large proportion of patients with Parkinson's disease develop diabetic nephropathy. A meta-analysis revealed a bidirectional association between diabetic nephropathy and depression. Similarly, a Japanese survey reported that the progression of diabetic nephropathy might increase the risk and severity of depression[25]. In cases of diabetic nephropathy, patients require long-term medication or insulin injections to control their blood glucose. Prolonged exposure to this disease can exacerbate depression. This depressive state may make patients less able to self-regulate and less aware of health protection, thereby exacerbating their overall medical condition, which can lead to progressive kidney failure.

Proteinuria is a risk factor of CVD. Advanced kidney disease can be exacerbated by CVD, leading to higher levels of depression[26]. Thus, a history of CVD is also a risk factor for depression in older patients with CKD[27]. The incidence of CVD tends to increase significantly with age; therefore, older patients with CKD are more likely to experience cardiovascular events that can exacerbate depression than the general population.

The relationship between anemia and depression

Anemia is a common complication in patients undergoing peritoneal dialysis and is caused by reduced erythropoietin production, toxin accumulation-induced erythropoietic depressants, shortened erythrocyte survival, and iron deficiency. Anemia is significantly associated with quality of life, CVD, hospital admissions, cognitive impairment, and death. In addition, patients with anemia often exhibit poor concentration and may also experience syncope and myocardial infarction, which can seriously affect their normal life and work[28]. Increased dyspnea and fatigue due to anemia may lead to a substantial decrease in physical and social activity, which in turn may increase depression. Hemoglobin and albumin levels serve as markers for anemia, and these two indicators were among the risk factors for depression in older patients with CKD, with a significantly higher incidence of depression in patients with anemia than in patients who did not present this condition.

Strengths and limitations

A strength of this study is its retrospective design, which enabled the analysis of independent risk factors associated with depression in older patients with CKD, providing a wider understanding of the patients' condition. Through correlation and logistic regression analyses, involving various factors associated with the incidence of depression in patients with CKD, the study compiled robust evidence, lending to more reliable results.

A limitation of this study is the absence of a comparative analysis involving other age groups. Therefore, the applicability of the study's findings is limited to the older adult population. However, at this stage, CKD patients are predominantly old. Although we believe that our findings can be generalized to other age groups, further studies are warranted to validate these hypothesis.

CONCLUSION

This study evidenced that years of education, sleep quality, anxiety status, comorbid DM, CVD, and anemia were independent risk factors for depression in older patients with CKD. Moreover, clinical management of older patients with CKD should address these risk factors to prevent depression and improve their prognosis.

ARTICLE HIGHLIGHTS

Research background

Previous studies demonstrated that over 20 million people in China experience decompensated kidney function, with 19.25% of them being older adults. Given the trend in global aging population, the proportion of older patients with chronic kidney disease (CKD) is expected to increase. Therefore, special attention should be focus on the treatment and prognosis of older patients with CKDs.

Research motivation

This study aimed to investigate the independent risk factors for depression in older patients with CKD undergoing peritoneal dialysis.

Research objectives

The study aimed to provide a clinical basis for the prevention of depression in older patients with CKDs.

Research methods

This retrospective study included a primary study population of 170 patients with CKD who received peritoneal dialysis from January 2020 to December 2022. We assessed the patients' mental status using the Beck Depression Inventory Score-II, Self-Rating Anxiety Scale, Anxiety Inventory Score, and the Pittsburgh Sleep Quality Index. Logistic regression was employed to identify depression independent risk factors among these patients.

Research results

The results of this study suggest that years of education, sleep quality, anxiety status, comorbid diabetes, cardiovascular diseases, and anemia are independent risk factors for depression in older patients with CKDs.

Research conclusions

This study found that years of education, sleep quality, anxiety status, comorbid diabetes mellitus, cardiovascular disease, and anemia were independent risk factors for depression in older patients with CKDs, and future clinical management of patients should address these risk factors to prevent depression and improve prognosis.

Research perspectives

This study investigated the independent risk factors for depression in older patients with CKD to provide a scientific basis for improving their prognosis, as well as to reduce the risk of depression in old age.

FOOTNOTES

Author contributions: Sheng YP, Ma XY, Liu Y, Yang XM and Sun FY designed the research; Sheng YP, Sun FY, Ma XY performed the research; Liu Y and Yang XM contributed new reagents/analytic tools; Sheng YP, Sun FY and Liu Y analyzed the data; Sheng YP, Sun FY and Ma XY wrote the paper.

Institutional review board statement: This study has passed the ethical review and approval of Cangzhou Central Hospital.

Informed consent statement: The study has obtained informed consent from the patient or the patient's guardian.

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Correlation analysis of mental health conditions and personality of patients with alcohol addiction

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Abstract

BACKGROUND

Alcohol addiction, or alcohol dependence, refers to a psychological state of strong craving for alcohol caused by drinking when both the drinking times and alcohol consumption reach a certain level. Alcohol addiction can cause irreversible damage, leading to mental illness or mental disorders, negative changes in their original personality, and a tendency to safety incidents such as committing suicide or violent attacks on others. Significant attention needs to be given to the mental health of alcohol addicts, which could reflect their abnormal personality traits. However, only a few papers on this issue have been reported in China.

AIM

To investigate the correlation between mental health and personality in patients with alcohol addiction.

METHODS

In this single-center observational study, we selected 80 patients with alcohol addiction as the research subjects, according to the criteria of the K10 scale to evaluate the mental health of patients with alcohol addiction, and divided these patients into four groups based on the evaluation results: Good, average, relatively poor and bad. And then analyzed the correlation between mental health conditions and personality characteristics from these four groups of patients.

RESULTS

The average score of the K10 scale (Kessler 10 Simple Psychological Status

Assessment Scale) in 80 patients with alcohol addiction was 25.45 points, the median score was 25 points, the highest score was 50 points, and the lowest score was 11 points. *Pearson*'s analysis showed that the K10 score was positively correlated with the scores of these two subscales, such as the P-subscale and the N-subscale ($P < 0.05$). In contrast, the K10 score had no significant correlation with the scores from the E-subscale and the L-subscale ($P > 0.05$).

CONCLUSION

The mental health conditions of patients with alcohol addiction are positively correlated with their personality characteristics.

Key Words: Alcohol addiction; Mental health; Personality characteristics; Public health; Patients; Correlational analysis

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Core Tip: Alcohol addiction, as a special behavioral pattern, can cause serious mental and physical burdens, and therefore must be highly valued. This article aims to explore the correlation between the formation of alcohol addiction as a behavioral pattern and personality. By randomly grouping alcohol addicted patients and evaluating their mental health using the K10 scale, the results showed that the mental health status of alcohol addicted patients was positively correlated with their personality traits.

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INTRODUCTION

Alcohol addiction, or alcohol dependence, refers to a psychological state of strong craving for alcohol caused by drinking when both the drinking times and alcohol consumption reach a certain level. Alcohol addicts may get to the point of failing to control their drinking behavior, and a series of physical tolerance or withdrawal symptoms will appear[1]. These reactions will manifest as the patient's compulsive craving for alcohol. After the cessation of drinking behavior, some physical withdrawal symptoms may occur, such as palpitations, trembling, and dyspnea, or psychological withdrawal symptoms, such as anxiety, depression, and delusions of victimization. The above symptoms could disappear with the resumption of the drinking behavior[2]. Alcohol addiction is a disease that is difficult to cure, with a high prevalence rate and a high rate of relapse. According to data from the World Health Organization in 2018[3], approximately 237 million men and 46 million women worldwide suffered from alcohol dependence syndrome. The data shows that, in 2018, the annual drinking volume per capita in Chinese was 7.14 L, the annual drinking volume per capita in Northern American countries was 9.71 L, the annual drinking volume per capita in Western Europe countries was 11.13 L, and the yearly drinking volume per capita in Australia was 10.47 L. The proportion of heavy drinkers among China adults was 22.6%. The proportion of heavy drinkers among North American adults was 25.7%; among Western European adults was 30.5%; and among Australian adults was 34.4%[3].

According to the World Health Organization, health is defined as the absence of disease or being free of infirmity and the balanced and normal state of physical, psychological, and social[4]. Mental health is one of the most important public health issues in the world all the time. Psychological health, like physical health, can also affect the life quality of individuals; this fact should be prompting people to pay more attention to mental illness as to physical diseases[5]. Alcohol addiction can cause irreversible damage to the physical status, psychological conditions, and social adaptations of patients who suffer from it. It results in mental illness or mental disorders, causing negative changes in their original personality characteristics[6] and leading to vicious public safety incidents such as committing suicide or launching violent attacks on others. It is important to pay attention to the mental health of people with alcohol addiction.

Personality is the organic unity of the dynamic internal organization and the corresponding behavior patterns formed by individuals in various interactions. It is a complex structural system, mainly including two aspects; the tendency of personality and the rational characteristics of personality, the former is the driving force of personality, and the latter refers to the differences that exist among individuals[7]. In addition to physical damage like alcoholic liver disease, long-term heavy drinking can disturb their social adaptation and potentiate negative personality changes[8]. Alcohol addiction is strongly associated with personality disorders[9,10]. Personality disorders are considered important factors in the pathogenesis, persistence, and outcome of alcohol dependence in patients with these pernicious features[11].

The mental health condition of individuals is closely related to their personality characteristics. The mental health of alcohol addicts may reflect their unique but abnormal personality traits. However, at present, few related research has been reported in China. Based on this, this study aimed to investigate the correlation between mental health status and personality characteristics in people suffering from alcohol addiction.

MATERIALS AND METHODS

Research subject

In this single-centered observational study, we selected 80 patients with alcohol addiction treated in our hospital from January 2022 to January 2023 as the research subjects. And the inclusion criteria were the following: (1) Patients clinically diagnosed with alcohol addiction[12]; (2) The patient being aware and consciously participating in the investigation; and (3) The patient able to fill out the questionnaire independently or with the help of an investigator. Exclusion Criteria: (1) Patients with other serious illnesses that may affect their psychological condition (such as disability, cancer, *etc.*); (2) Patients with severe mental disorders that could impact affect the accuracy of the study; and (3) Those who are unwilling to cooperate with the investigation standards. All proceedings were carried out per the *Declaration of Helsinki*.

General demographic information questionnaire

The content of the questionnaire mainly included; (1) The basic personal information on alcohol addicts; their gender, age, marital status, education level, *etc.*; (2) The participants' financial situation, including the self-assessment of the financial level, whether they are autonomous, and whether they were indebted; (3) Daily life behaviors of patients, whether smoking, suffering from a sleep disorder, maintaining a good frequency of daily exercise, *etc.*; (4) The number of years set to the establishment of the alcohol addiction; and (5) Other related psychological conditions, including whether they had close friends to talk to, whether they encountered major setbacks or unfortunate situations, *etc.*

Mental health rating scale (K10)

The K10 scale[13], developed by Kessler and Mrocze of the University of Michigan, assesses patients' mental health and can screen for self-management scoring scales on the population's psychological status risk factors[14]. The scale is convenient to operate, owns the non-specific character in assessment, and has been widely used in the survey of mental health group in the United States, Canada, and other countries. The K10 scale contains ten items about anxiety, depression, and stress levels experienced in the last four weeks before the assessment. These are: (1) How often do you feel tired for no reason? (2) How often do you feel nervous? (3) How often do you feel nervous, and nothing else can calm you down? (4) How often do you feel hopeless about life? (5) How often do you feel uneasy and irritable? (6) How often do you feel restless and irritable so that it is difficult for you to calm down? (7) How often do you feel depressed? (8) How often do you feel strenuous when doing anything? (9) How often do you feel sad and nothing can interest you? and (10) How often do you you're your existence as meaningless? To each question corresponds five response criteria and scored in this manner; 5 points for "all time," 4 for "most of the time," 3 for "sometimes," 2 for "occasionally present," and 1 for "almost nonexistent." The total score is calculated according to the respondent's responses, with a score ranging from 10 to 50 points, where a maximum of 50 points could indicate that the patient has serious psychological distress, and a minimum score of 10, indicates that the patient has no psychological distress. This study was designed according to previous assessment criteria, and the overall score was classified into four levels: 10-19 points at the first level, which represented good mental health; level 2, 20-25 points, representing average mental health; level 3 score of 26-29, which represented relatively poor mental health; a score of 30-50 on a fourth scale represented bad mental health. The evaluation items of the K10 scale mainly focused on the two routine measurements such as anxiety and depression, which ascertain the degree of anxiety, depression, and life stress of the respondent during the previous four weeks and contribute to analyzing the population's mental health.

Eysenck personality questionnaire

Compiled by Eysenck in 1952, revised by Professor Gong Yaoxian in 1983, and formed a Chinese edition. The adult version of the questionnaire consists of four subscales, psychotropic (P), extrovert (E), neuroticism (N), and lie (L), with 88 questions[15]. Among them, psychopathic tendencies are reflected by the P dimension, introversion and extroversion are reflected by the introvert-E dimension, emotional stability is reflected by the N dimension, and the L tendency is used as an effectiveness scale. The P, E, N, and L scales include 23, 21, 24, and 20 items in the adult questionnaire, each of which only answers "yes" and "no," with 1 point per question. Among them, the introvert-E: A high score indicates that the person is extroverted, emotionally impulsive, adventurous, and good at interacting with people. A low score can indicate introversion, emotional stability, taciturn, indifference to people, quietness, introspection, and conformity. N: A high score would suggest depression, anxiety, preoccupation, emotional instability, and sometimes irrationality. Mental quality (P): High scores may indicate delayed reaction, being withdrawn and lazy, having no contact with anyone, being emotionally cold, poorly adaptable, eccentric and bizarre, and being incongruous with the environment. L: A high score indicates it is disguised and untrue. Disguise itself has a stable personality function related to various elements of other people. In this study, Cronbach's α of the P, E, N, and L subscales were 0.71, 0.78, 0.87, and 0.71, respectively.

Statistical analysis

SPSS22.0 statistical software was used to analyze and process data. Continuous variables were confirmed by the normality test and homogeneity test for variance, and it determined that they have the homogeneity of variance based on approximately normal distribution, expressed as mean ± SD, *t*-test, and ANOVA (analysis of variance). Categorical variables expressed as percentages, chi-square test, Fisher exact test or Mann-Whitney test, the correlation using *Pearson* correlation analysis, and taking the result of $P < 0.05$ to indicate that the difference was statistically significant.

Biostatistics statement: The statistical methods of this study were reviewed by the clinical research office from the corresponding author's institution prior to the submission.

RESULTS

General demographic information of patients with alcohol addiction

Eighty patients with alcohol addiction were included in this study, 67 male patients, 13 female patients, aged 20-65 years, and the duration of the addiction was 5-30 years. For other information (Table 1).

Analysis of mental health status of patients with alcohol addiction

The average K10 score of the 80 patients with alcohol addiction was 25.45, with a median score of 25, with the highest score being 50 and the lowest being 11. A score of K10 between 10 and 19 indicated that the patient's mental health was good (Grade 1, low risk of mental illness) in 17 people, accounting for 21.25%; A score of K10 on a score of 20-24 indicated that the patient's mental health status is average (Grade 2, low risk of mental illness), and there are 20 people in this group, accounting for 20.00%; A K10 score of 25-29 indicated that the patient's mental health is poor (Grade 3, higher risk of mental illness) in 32 people, accounting for 40.00%; A K10 score of 30-50 indicated that the patient's mental health is poor (Grade 4, high risk of mental illness) in 11 people, accounting for 13.75% (Table 2).

Analysis of personality characteristics of patients with alcohol addiction

The scores of the two subscales, including P-subscale and N-subscale in the 10-19 group, 20-24 group, 25-29 group, and 30-50 group of the K10 score, were statistically significant ($P < 0.05$). In contrast, the overall comparison of scores in E-subscale and L-subscale was not statistically significant ($P > 0.05$). Among them, the scores of the P-subscale were compared in the following groups, the 10-19 groups, and the 20-24 groups were smaller than the 25-29 groups and 30-50 groups, and the differences were statistically significant ($P < 0.05$). About the comparison in N-subscale scores, 10-19 groups < 20-24 groups < 25-29 groups, and 30-50 groups, and the differences were statistically significant ($P < 0.05$) (Table 3).

Correlation analysis of mental health conditions and personality characteristics

Pearson's analysis showed that the K10 score was positively correlated with the scores of the P-subscale, N-subscale, and other two subscales ($P < 0.05$). In contrast, the K10 score had no significant correlation with the scores of E-subscale and L-subscale ($P > 0.05$) (Table 4 and Figure 1).

DISCUSSION

Alcohol dependence, namely alcohol addiction, is a chronic and recurrent encephalopathy characterized by compulsive, intense cravings for alcohol, loss of control over alcohol use, and negative emotions and physical discomfort that will emerge when alcohol is unavailable. Harmful use of alcohol is one of the largest risk factors for death, disease, and disability[15-18]. The *Global Report on Alcohol Use and Health WHO in 2018* states that[3] in 2016, the global prevalence of alcohol use disorders (AUD) among people aged 15 and above reached 5.1%, and the prevalence of alcohol dependence in this age group reached 2.6%. The harmful use of alcohol caused approximately 3 million deaths worldwide in the same year, accounting for 5.6% of all deaths. According to the 2019 survey of Chinese groups of mental illnesses, the 12-month prevalence of AUD in China was 1.8%, and the lifetime prevalence was 4.4%, of which the 12-month prevalence of alcohol dependence was 0.7% and the lifetime prevalence was 1.3%[19]. Alcohol abuse can cause damage to multiple systems, including the nervous system, cardiovascular system, digestive system, respiratory system, *etc.* Long-term drinking can also cause the breakdown of family relationships, disturb normal work, and cause accidents after drinking that seriously endanger personal and social safety. Exploring the mechanisms of addiction in alcohol dependence, actively seeking new treatment options, and encouraging patients with alcohol dependent to receive professional treatment for alcohol withdrawal would be essential methods to reduce the harm due to alcohol abuse[20].

Addictive substances such as alcohol can activate the brain's reward system, and the reward hypothesis is a widely accepted neurobiological hypothesis of addiction[21]. The central nervous system can produce a rewarding effect on natural rewards, such as food, sex, *etc.*, thereby maintaining the continuity of the species. Almost all addictive substances can stimulate the brain's reward circuit, making it faster and more intense than natural rewards, resulting in intense pleasure in the individual. Positron emission tomography studies have shown that drunken doses of alcohol can promote the release of dopamine and opioid peptides from the brain to the ventral striatum, and rapid and high amounts of dopamine in the midbrain limbic system are associated with the subjective feeling of "hi," which is the rewarding effect [22]. Individuals associate alcohol use with positive rewards, which is positive reinforcement. The neurotransmitters and neuromodulators involved in alcohol reward include not only dopamine but also the opioid peptides, γ-aminobutyric acid, glutamic acid, serotonin, acetylcholine, and endocannabinoids acting on the ventral tegmental area or nucleus accumbens[23,24].

Patients with alcohol addiction are given to addictive substances, which greatly affect their mental health and personality characteristics. Jung[25] used the California Personality Questionnaire to implement the longitudinal measurement on adolescents who initially did not have drinking problems. Comparing boys who later developed drinking problems with the control group without similar issues, it was found that male alcohol addicts exhibited more rebellion and extroversion than others before they started drinking. While among female subjects, heavy drinkers showed more pessimism, introversion, and dependence as adolescents than light drinkers[25]. Cloninger *et al*[26] followed 431 subjects longitudinally for 16 years using a Three-dimensional Personality Questionnaire, which played an important role in clarifying the relationship between personality characteristics and alcohol abuse[26]. Cloninger *et al*[26] evaluated the

Table 1 The general demographic information of patients with alcohol addiction, *n* (%), mean ± SD

Variable	Number of cases (*n* = 80)	Constitution ratio (%)
Age		
< 50	47	58.75
≥ 50	33	41.25
Female	13	16.25
Man	67	83.75
Level of education		
Primary school and below	25	31.25
Junior high school and Senior high school	49	61.25
University and above	6	7.50
Marital status		
Married	51	63.75
Unmarried	9	11.25
Divorced or widowed	20	25.00
Self-evaluation of economic abundance		
Yes	31	38.75
No	49	61.255
Liabilities		
Yes	33	41.25
No	47	58.75
Smoking		
Yes	53	66.25
No	27	33.75
Sleep disorders		
Yes	46	57.50
No	34	42.50
Daily exercise		
Often	20	25.00
Sometimes	31	38.75
Never	29	36.25
The number of years set for getting ill		
≤ 5	24	30.00
6-10	34	42.50
≥ 11	22	27.50
Close friends		
Yes	28	35.00
No	52	65.00
Major setbacks or unfortunate situations		
Yes	57	71.25
No	23	28.75

Table 2 Analysis of mental health status of patients with alcohol addiction, *n* (%)

K10 Score	Number of cases	Percentage (%)
10-19	17	21.25
20-24	20	20.00
25-29	32	40.00
30-50	11	13.75
Total	80	100.00

Table 3 Analysis of personality characteristics of patients with alcohol addiction, mean ± SD

K10 scores	P	E	N	L
10-19 (n = 17)	6.34 ± 1.01[b,c]	7.51 ± 1.07	8.88 ± 2.72[a,b,c]	15.55 ± 2.31
20-24 (n = 20)	6.91 ± 1.40[b,c]	7.77 ± 2.06	11.84 ± 2.81[b,c]	15.18 ± 3.06
25-29 (n = 32)	8.98 ± 1.86	8.25 ± 1.91	14.72 ± 4.24	14.81 ± 3.47
30-50 (n = 11)	9.71 ± 1.67	8.42 ± 2.29	15.36 ± 2.11	15.61 ± 1.90
F	17.920	0.869	13.670	0.328
P value	< 0.001	0.460	< 0.001	0.804

[a]P < 0.05 comparison with the 20-24 groups.
[b]P < 0.05 comparison with the 25-29 groups.
[c]P < 0.05 comparison with the30-50 groups.
P: Psychotropic; E: Extrovert; N: Neuroticism; L: Lie.

Table 4 Correlation analysis of mental health conditions and personality characteristics

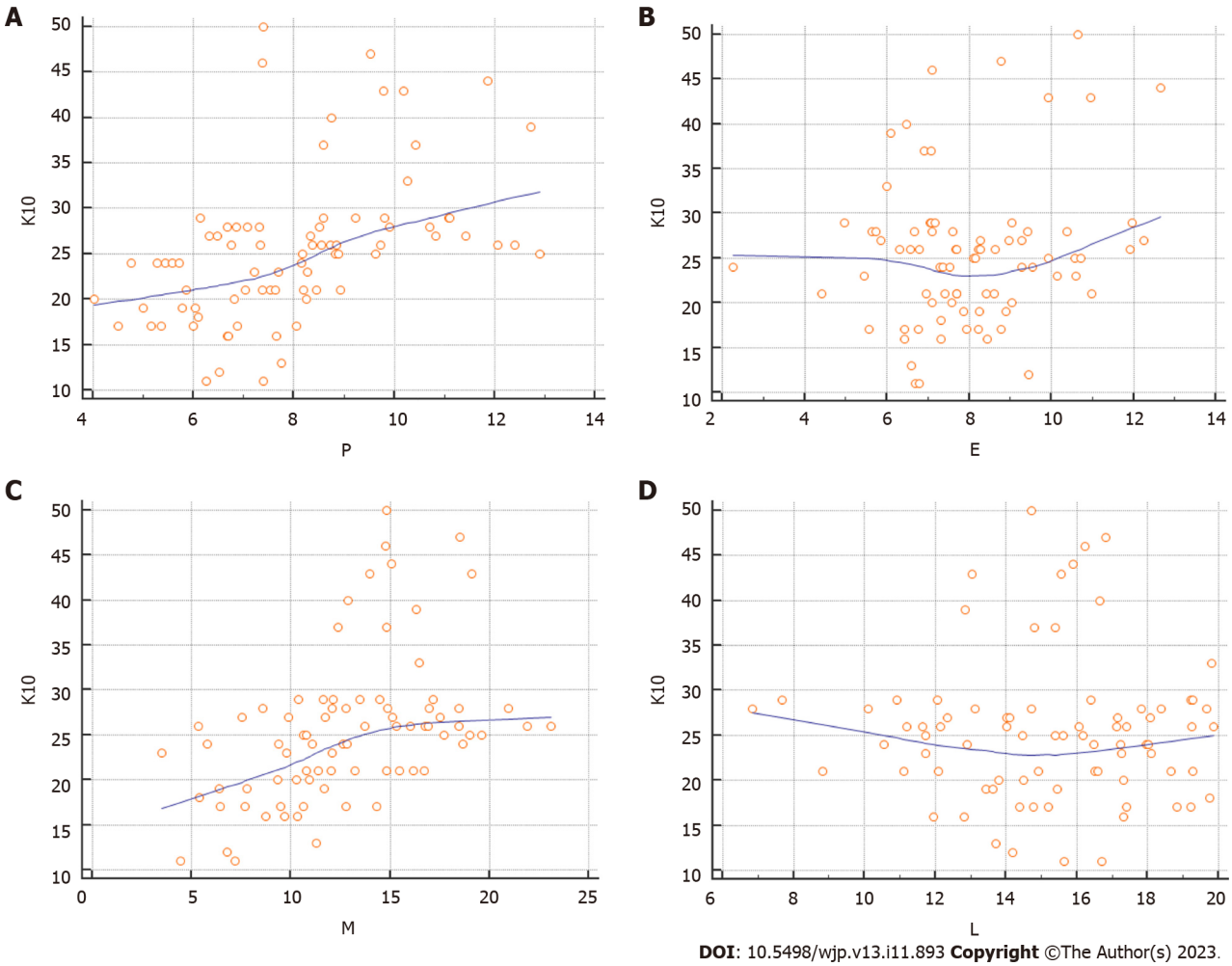
Item	*r* value	*P* value
P	0.477	< 0.001
E	0.201	0.074
N	0.454	< 0.001
L	-0.013	0.904

P: Psychotropic; E: Extrovert; N: Neuroticism; L: Lie.

participants' personality characteristics at 11 by behavioral assessment; Participants were then assessed for alcohol addiction at 27. The results showed that high sensation seeking and low harm avoidance were risk traits for alcohol addiction and that participants with these two traits in childhood were 20 times more likely to experience alcohol addiction in adulthood than those without these two traits. The thesis of De la Rosa-Cáceres *et al*[27] in 2022 noted that medium-to-high-risk personality characteristics in participants correlated with the diagnostic criteria for alcohol addiction[27]. Labouvie and McGee[28] conducted longitudinal studies of subjects aged 12 to 21 years, reaffirming that personality predicts alcohol and substance abuse and that adolescents with early substance abuse scored with a low degree on fulfillment, cognitive structure, and avoidance of harm but scored with a high degree on relationships, independence, depression, impulsivity, and play[28]. Gmel *et al*[29] analyzed the questionnaire results in 5125 young men and pointed out that high impulsivity and sensory seeking are also risk factors for alcohol addiction.

The results of this study showed that the K10 score of patients with alcohol addiction was positively correlated with the scores of two subscales such as P-subscale and N-subscale (r = 0.477, 0.518, 0.454, P < 0.05), patients with higher K10 scores had higher scores in P-subscale and N-subscale. The personality characteristics of those with high scores on the P-subscale presented social withdrawal trait, with strange behaviors like apathy and poor control. Herein, they responded strongly to various stimuli. People with high scores on N-subscale often have overt nervousness, fear, terror, irritability, restlessness, anxiety, depression, and panic; when these people encounter abnormal psychosocial problems, they are more difficult to extricate themselves than ordinary people and will be worried, depressed, and hesitant.

Alcohol-dependent patients with higher scores on P-subscale on the eysenck personality questionnaire (EPQ) score tend to have personality characteristics such as isolation, isolation, bizarre behavior, apathy, poor control, and therefore strong responses to various stimuli[30-32]. The reason may be that individuals who are withdrawn and introverted when



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Figure 1 The correlation between the K10 score and the subscale score. A: P-subscale score; B: E-subscale score; C: N-scale score; D: L-scale score. P: Psychotropic; E: Extrovert; N: Neuroticism; L: Lie.

they encounter unsatisfactory and unpleasant life events in daily life are neither good at alleviating their bad emotions by confiding inward troubles and depression to others, nor can they self-regulate through healthy and effective coping, so it is easier to apply the simple, direct but self-anesthesia method of drinking because of "Quench a thirst with poison" to avoid the bad reality, which is the so-called "Drinking can relieve thousands of worries." It might achieve certain results in the short term. Although individuals can also realize that long-term drinking could harm their bodies due to poor self-control. When they reencounter unsolvable life problems, they will involuntarily apply the so-called "effective" method as before, that is, "drinking." Consequently, they enter a vicious circle, increasing the possibility of "alcohol dependence." In addition, if the individual's sensitivity is high and it is easy to have a strong rational response to various stimuli, especially in the trivial matters of life, then it will be easier for them to all day long bothered by life dissatisfaction, which increases the possibility of "drinking" as a bad coping style. Moreover, patients with alcohol dependence due to long-term drinking habits will undergo certain changes. They will no longer care about their family, life, and work, having no emotional expression on their families and friends, just immersed in the "anesthesia" of alcohol all day. The general social interaction cannot interest them. Naturally, they will be like outliers and indifferent to anything. The patient will also have "foraging" behavior; that is, the patient will take all possible ways to find alcohol and meet the purpose of their drinking in the process of the patient's "foraging" in juncture to the conventional way. It may also include unconventional methods such as "Proposing a toast," "Cheating others to drink," "Gifting alcohol as private bribery," "Stealing alcohol," *etc.* these strange behaviors usually do not appear in normal individuals and represent the embodiment of "Weird behaviors."

Patients with alcohol dependence with higher N scores in the EPQ questionnaire had more obvious personality characteristics such as nervousness, fear, fear, irritability, restlessness, anxiety, depression, panic, anxiety, anxiety, depression, depression, and indecision[32-34]. The reasons could be that when individuals with tense, fearful, and indecisive personalities deal with life events, they are prone to cause difficulties in dealing with them correctly and in time due to their personality defects. When faced with choices in life, they will also miss the best time of choice and decision because of their indecision, so they might often fall into self-regret and afterward complain. Although individuals have also tried to apply healthy coping methods for solving problems, because of their nervous, fearful, and hesitant personality. These healthy coping styles are difficult to succeed in, so individuals will easily apply bad coping methods such as "drinking" to solve their adverse reactions. For individuals, "drinking" can not only solve the current dilemma in the short term, but

more importantly, it does not require too many personality characteristics and self-effort and successfully "avoids" the "negative influence" and "self-denial" brought about by their bad personality characteristics in the process of solving problems. Therefore, when individuals encounter similar life difficulties and other adverse conditions in the future, they will naturally use "drinking" to deal with it, which lays a certain foundation and conditions for forming later "alcohol dependence." In addition, if the individual's attitude to life is more negative, the individual is prone to be dissatisfied and disappointed with life and the future and will adopt more avoidance coping methods to deal with bad emotions and produce a sense of self "abandoned" by the world. At this time, the individual cannot solve his inner depression and resentment, and it is easy to use “drinking” to escape reality and self-anesthetize, and over time, the possibility of "alcohol dependence" will increase.

CONCLUSION

However, there were some limitations worth highlighting in this study. Firstly, the size of the sample studied was relatively smaller. And secondly, because this research was a single-center-based study, thus, the selection of these patients was limited to the scope of the patients in this hospital, which may have brought some biases in the interpretation of the results. Therefore, it appears necessary to design a larger, multi-center and multiethnic sample to further analyze and probe into the results of this study with an in-depth and sophisticated method.

ARTICLE HIGHLIGHTS

Research background

Correlation analysis of the correlation between alcohol addiction behavior and personality traits, exploring the causes of this behavior pattern, and thus serving the clinical treatment of alcohol addiction.

Research motivation

Alcohol addiction behavior is related to the personality characteristics of patients, and psychotropic (P) and neuroticism (N) dimensions of personality can positively induce alcohol addiction behavior.

Research objectives

There is a positive correlation between the scores of mental health assessment and the scores of P and N dimensions in personality assessment.

Research methods

Using the K10 Mental Health Assessment Scale, analyze the mental health status of alcohol addiction patients and its correlation with personality.

Research results

Based on existing research on the mental health of alcohol addiction, explore the correlation between the occurrence of alcohol addiction behavior and self-personality.

Research conclusions

Based on the existing talent gap of clinical research nurses, the training scheme of nurses should be scientifically customized to promote the development of clinical trials.

Research perspectives

Alcohol addiction, as a serious pattern of physical and mental harm, can lead to irreversible harm in severe cases. However, research reports on the causes of alcohol addiction behavior are not yet clear.

FOOTNOTES

Author contributions: Liu Y and Zhang XL contributed to the conceptualization; Liu Y and Cheng J performed the data curation; Pang LJ and Cheng J contributed to the formal analysis; Liu Y wrote the original draft; Zhang XL wrote the review and editing.

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ORIGINAL ARTICLE

Retrospective Study

Anti-infective therapy durations predict psychological stress and laparoscopic surgery quality in pelvic abscess patients

Rui-Rui Zhang, Lei Zhang, Rui-Heng Zhao

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Abstract

BACKGROUND

The degree of psychological stress and the difficulty and efficacy of laparoscopic surgery differ in patients with pelvic abscesses after different durations of anti-infection treatment.

AIM

To compare and analyse the effects of different durations of anti-infective therapy on patients' preoperative psychological stress level and the clinical efficacy of laparoscopic surgery in patients with pelvic abscesses to offer a reference for the selection of therapy plans.

METHODS

A total of 100 patients with pelvic abscesses who were admitted to the Department of Gynecology of Suzhou Ninth Hospital affiliated to Soochow University (Suzhou Ninth People's Hospital) from January 2018 to December 2022 were retrospectively enrolled. According to the different durations of anti-infective therapy, they were divided into Group S (50 patients, received anti-infective therapy for 24-48 h) and Group L (50 patients, received anti-infective therapy for 48-96 h). Baseline data, state-trait anxiety score at admission and before surgery, self-rating anxiety scale (SAS) + self-rating depression scale (SDS) score, surgery time, adhesion grading score, intraoperative blood loss, presence or absence of intraoperative intestinal injury, ureteral injury or bladder injury, postoperative body temperature, length of hospital stay, and presence or absence of recurrence within 3 mo after surgery, chronic pelvic pain, incision infection, dysmenorrhea, menstrual disorder or intestinal obstruction were compared between the S group and the L group.

RESULTS

There was no significant difference in the background data between the S group

and the L group ($P < 0.05$). There was no significant difference in the state-trait anxiety score or SAS + SDS score between the S group and the L group on admission ($P < 0.05$). The state-trait anxiety score and SAS + SDS score of the S group were lower than those of Group L after receiving different durations of anti-infective therapy ($P < 0.05$). There was no significant difference in the incidence of intestinal, ureteral or bladder injury between the S group and the L group ($P < 0.05$). The surgery time of Group S was shorter than that of Group L, and the adhesion score and intraoperative blood loss volume were lower than those of Group L ($P < 0.05$). There was no significant difference in the incidence of incision infection, dysmenorrhea, menstrual disorder or intestinal obstruction between the S group and the L group ($P < 0.05$). The postoperative body temperature of Group S was lower than that of Group L ($P < 0.05$), and the hospital stay was shorter than that of Group L ($P < 0.05$). The incidences of recurrence and chronic pelvic pain within 3 mo after surgery were lower than that of Group L ($P < 0.05$).

CONCLUSION

Twenty-four to forty-eight hours of anti-infective therapy is better than 48-96 h of anti-infective therapy for patients with pelvic abscesses because the degree of psychological stress is lower, which is more conducive to achieving better outcomes after laparoscopic surgery.

Key Words: Anti-infective therapy; Pelvic abscesses; Psychological stress; Laparoscopic surgery; Efficacy

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Core Tip: A pelvic abscess is a typical manifestation of pelvic inflammatory disease that can endanger the patient's life in severe cases. Here, we analysed the data of 100 patients with pelvic abscesses and divided them into Group S (anti-infective treatment for 24-48 h) and Group L (anti-infective treatment for 48-96 h) according to different durations of anti-infection. Through statistical analysis of the data of the two groups of patients, the authors researched the effects of different durations of preoperative anti-infective therapy on the psychological stress of patients and the postoperative effects of laparoscopic surgery in China to select the optimal duration of anti-infective therapy.

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INTRODUCTION

One of the most common serious infections in nonpregnant women of childbearing age is pelvic inflammatory disease (PID)[1]. PID is caused by mixed microbial infections of the upper reproductive tract, predominantly affects sexually active young women, and may be asymptomatic or present with tubuloovarian abscesses, which may be life threatening [2]. One of the most prevalent types of pelvic abscesses in women of childbearing age is tubo-ovarian abscesses. The best therapy for pelvic abscesses should be safe, effective, economical, minimally invasive, and have minimal effect on female fertility. Salpingo-ovarian abscesses have traditionally been treated with broad-spectrum antibiotics[3]. Long-term conservative therapy with drugs and long-term repeated use of antibiotics often lead to chronic pelvic abscesses or secondary adhesion, which decreases the patient's fertility, causes chronic pelvic pain, and seriously affects quality of life. Surgical intervention is required for patients who fail to receive conservative therapy. Except for a few patients with low-lying abscesses and a palpable posterior fornical incision and drainage tube, surgery has replaced conservative drug therapy and has become the first choice for the treatment of pelvic abscesses. Laparoscopic surgery has less biological impact on the body but a stronger protective effect on the immunity of the body, thereby reducing the incidence of infectious complications[4,5]. Preoperative anti-infective therapy can limit lesion development, prevent the spread of inflammation, and improve the efficacy of surgery. However, clinical observation shows that different durations of anti-infective therapy have different effects on surgery and postoperative outcomes. In our study, the data of 100 patients with pelvic abscesses who were admitted to our hospital in recent years were collected, and the differences in the outcomes of anti-infective therapy administered preoperatively, intraoperatively or postoperatively for different durations in patients with pelvic abscesses were analysed to find a more appropriate duration of anti-infective therapy.

MATERIALS AND METHODS

Patient characteristics

Data from a total of 100 patients with pelvic abscesses who were admitted to our hospital from January 2018 to December 2022 were retrospectively collected. According to different durations of anti-infective therapy, they were divided into

Group S and Group L. Group S was treated with anti-infective therapy for 24-48 h, and Group L was treated with anti-infective therapy for 48-96 h. There were 50 patients in Group S and 50 patients in Group L.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with pelvic abscesses that were diagnosed by symptoms, physical examination, ultrasound, routine blood examination and vaginal fornix puncture; (2) Patients undergoing elective laparoscopic surgery who were treated with sulperazon plus ornidazole for anti-infection treatment before surgery; (3) Patients who received anti-infective therapy and were evaluated with the state-trait anxiety[6], self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scales[7]; and (4) Patients with complete data.

The exclusion criteria were as follows: (1) Patients with blood diseases or infectious diseases, who were pregnant or lactating, or with mental disorders or severe organ failure; (2) Patients with ruptured pelvic abscesses or who received other antibiotics before antibiotic therapy; and (3) Patients who refused to participate or had family members who were not supportive.

Patients and their relatives understood the content of our study and signed informed consent forms.

Methods

After the patients were diagnosed with pelvic effusion by examination, the Group S and the Group L were treated with sulperazon combined with ornidazole for anti-infective therapy; that is, according to the results of germ culture and drug sensitivity tests of puncture fluid, the patients were given 3.0 g sulperazon (H20020597; Pfizer Pharmaceuticals Co., LTD) and 0.25 g ornidazole (Hunan Jiudian Pharmaceutical Co., LTD). Both drugs were administered by intravenous drip twice every 24 h. Group S received 24-48 h of anti-infective therapy, while Group L received 48-96 h of anti-infective therapy. State-trait anxiety and SAS + SDS scores were obtained from both groups before and after admission.

After anti-infective therapy, laparoscopic surgery was performed in both groups. After general anaesthesia, the patient was intubated and mechanically ventilated to assist respiration, and the patient was placed in the head-down and bladder lithotomy position. After routine skin disinfection and skin draping, a 1 cm curved incision was made below the umbilical margin of the patient, and CO_2 pneumothorax was established with a pressure range of 10-12 mmHg. The laparoscope was placed in the abdomen, and surgery holes of 1 cm and 0.5 cm in size were cut at the left and right McHolley points of the lower abdomen, respectively. The exposed abscesses were incised, and pus and fragments were aspirated with an aspirator and sent to the laboratory. The surgical scope should be determined according to the patient's fertility requirements and the extent of the lesion and adjusted according to the patient's situation and needs. Patients with fertility requirements should undergo salpingostomy. After the surgery, normal saline and metronidazole solution were used to wash the pelvic cavity repeatedly, the patient's position was adjusted to head up and foot down, and the pelvic cavity was washed again. If the abscesses involved the fallopian tube, they were removed by bipolar coagulation, and haemostasis was performed. After abscess removal, the pelvis was flushed with 250 mL of 0.5% metronidazole solution, and a pelvic drainage tube was placed. According to the results of the germ culture and drug sensitivity test of abscess secretion, the corresponding antibiotics were given after the surgery. The body temperature was maintained at the normal level for 24 h. Then, oral antibiotics were administered for 1 to 2 wk.

Observation indicators

(1) The psychological stress of the patients in Group S and Group L was investigated by the scale at admission and before surgery. The state-trait anxiety score includes two parts: State anxiety (S-AI) and trait anxiety (T-AI). Each item is scored from 1 to 4 points, with positive emotions scored in reverse order. The total score of the S-AI and T-AI is 20 to 80 points. The higher the score, the higher the anxiety level. The SAS and SDS compiled by Zung[8,9] (the SAS/SDS self-rating scale includes 20 items, and each item is scored from 1 to 4; the higher the score, the greater the degree of psychological stress) were used to evaluate the patients; (2) Surgery time, adhesion score (the modified classification standard of adhesion of the American Society for Reproductive Medicine in 1996[10] was used to evaluate the extent, degree and nature of the adhesion during surgery), intraoperative blood loss, the presence or absence of intraoperative intestinal, ureteral and bladder injuries; and (3) Postoperative body temperature, length of hospital stay, and the presence or absence of recurrence within 3 mo after the surgery, chronic pelvic pain, incision infection, dysmenorrhea, menstrual disorder, or intestinal obstruction.

Statistical procedure

SPSS 26.0 was used for statistical analysis. Measurement data are expressed as the mean ± SD, and a *t* test was used. Count data are expressed as a percentage (%), the χ^2 test was used, and $P < 0.05$ was regarded as statistically significant.

RESULTS

The difference in baseline data

There was no significant difference in age, sex, body temperature, mass diameter or reproductive history between Group S and Group L ($P > 0.05$). As shown in Table 1.

The difference in psychological stress

There was no significant difference in the state-trait anxiety score or SAS + SDS score between the Group S and the Group

Table 1 Comparison of baseline data between the S group and the L group

Baseline data	Group S (*n* = 50)	Group L (*n* = 50)	t/χ^2	*P* value
Age (mean ± SD)	32.2 ± 4.1	33.9 ± 5.3	1.794	0.076
Duration disease (mo, mean ± SD)	14.7 ± 3.2	15.4 ± 2.9	1.146	0.255
Body temperature (°C, mean ± SD)	37.5 ± 1.5	37.7 ± 1.3	0.713	0.478
Diameter of mass (cm, mean ± SD)	5.9 ± 1.9	6.3 ± 1.6	1.139	0.258
Reproductive history [*n* (%)]	46 (82)	43 (86)	0.919	0.338

L at admission ($P > 0.05$). The state-trait anxiety score and SAS + SDS score of Group S were significantly lower than those of Group L after 24-48 h and 48-96 h of anti-infective therapy ($P < 0.05$) (Figure 1).

Differences in intraoperative clinical indicators

There was no significant difference in the incidence of intestinal, ureteral and bladder injuries between the Group S and the Group L ($P > 0.05$). The surgery time of Group S was shorter than that of Group L, and the adhesion score and intraoperative blood loss were lower than those of Group L ($P < 0.05$). As shown in Table 2 and Figure 2.

The difference in postoperative efficacy

There was no significant difference in the incidence of postoperative incision infection, dysmenorrhea, menstrual disorder, or intestinal obstruction between the Group S and the Group L after different durations of anti-infective therapy ($P > 0.05$). Postoperative body temperature was lower in Group S after 24-48 h of anti-infective therapy than in Group L after 48-96 h of anti-infective therapy ($P < 0.05$), and the hospital stay was shorter than that of Group L ($P < 0.05$) (Figure 3). The incidences of recurrence and chronic pelvic pain within 3 mo after surgery in Group S were lower ($P < 0.05$) than that in Group L (Table 3).

DISCUSSION

In the past, pelvic abscesses were often treated with conservative drug therapy[11], that is, long-term repeated use of antibiotics, because antibiotic therapy alone was not only ineffective in achieving a complete cure but could also cause the disease to develop into chronic PID or chronic pelvic abscesses, leading to secondary pelvic adhesion[12]. Therefore, surgery gradually replaced conservative therapy to become the main therapy method. In laparoscopic surgery, the advantages are the small incision, sufficient surgical field, no unnecessary interference, no exposure of abdominal organs to the air, less interference with the pelvic environment, less intraoperative blood loss, and fewer complications[13]. However, a pelvic abscess is an inflammatory reaction caused by a pathogenic bacterial infection. If surgical therapy is carried out directly after diagnosis, it is easy for inflammation to spread and affect the surgical outcome. Preoperative anti-infective therapy can control the spread of systemic inflammation, relieve pelvic abscesses, and facilitate a smooth course of surgery. However, there is no consensus on the optimal duration of preoperative anti-infective therapy.

In our study, the incidences of intraoperative injury and postoperative complications in Group S were lower than that in Group L, but the difference was not statistically significant, which may be related to the small sample size and individual differences between patients. However, the state-trait anxiety score and SAS + SDS score of Group S were statistically lower than those of Group L ($P < 0.05$), indicating that patients who received 24-48 h of anti-infective therapy had less preoperative psychological stress than those who received 48-96 h of anti-infective therapy. This may be because a long duration of preoperative anti-infective therapy diminishes patients' expectations for surgery or because patients have a misunderstanding of their illness. Stevens *et al*[14] showed that the higher the patients' preoperative expectations for surgery, the higher their depression and anxiety scores. Therefore, we speculated that with a prolonged anti-infection treatment time, patients' expectations of the operation effect increased, and they were more likely to have anxiety, depression and other psychological conditions. The study by Kılıç *et al*[15] showed that the longer the treatment time, the heavier the patients' psychological burden. According to this, we believe that a longer period of anti-infection treatment may make patients with pelvic abscesses think that preoperative preparation is not sufficient, their physical weakness cannot withstand the surgical trauma, or their disease will be suddenly worsened, thus causing them to experience worry, anxiety, depression and other adverse emotions. Therefore, we suggest that surgeons pay attention to patients who have undergone anti-infection treatment for an extended period before surgery or have anxiety and depression to be able to provide certain preoperative psychological education if necessary. However, after reviewing a large number of studies, we did not find any correlation between preoperative anti-infective treatment time and preoperative psychological state in patients with pelvic abscesses. Therefore, the specific relationship between preoperative anti-infective treatment time, psychological stress effect and surgical effect in patients with pelvic abscesses needs to be further investigated.

After 24-48 h of anti-infective therapy, the surgery time, adhesion score, intraoperative blood loss volume, postoperative body temperature was significantly lower and the hospital stay was significantly shorter in Group S than those in Group L ($P < 0.05$), indicating that compared with 24-48 h of anti-infective therapy, long-term anti-infective

Table 2 Comparison of intraoperative clinical indicators

Clinical indicators	Group S (n = 50)	Group L (n = 50)	t/χ^2	P value
Surgery time (min)	55.45 ± 16.48	78.78 ± 17.87	2.714	< 0.01
Adhesion score	3.17 ± 0.84	4.04 ± 0.49	6.326	< 0.001
Intraoperative blood loss (mL)	45.54 ± 11.94	72.15 ± 9.21	12.48	< 0.001
Intraoperative intestinal injury	1 (2.00)	3 (6.00)	1.042	0.307
Intraoperative ureteral injury	2 (4.00)	6 (8.00)	2.174	0.140
Intraoperative bladder injury	0 (0.00)	2 (4.00)	2.041	0.153

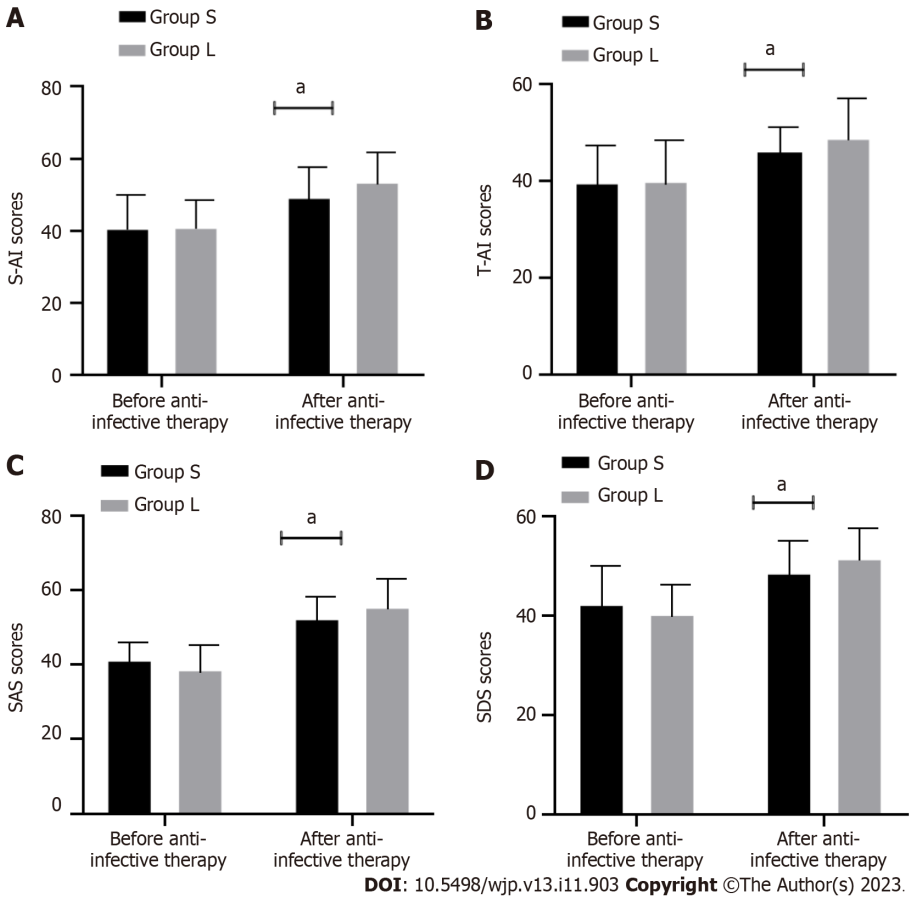
Table 3 Comparison of efficacy

Indicators	Group S (n = 50)	Group L (n = 50)	t/χ^2	P value
Postoperative body temperature	38.02 ± 0.98	38.94 ± 1.37	3.862	< 0.001
Length of stay (d)	7.68 ± 1.41	9.94 ± 2.01	6.509	< 0.001
Tumour recurrence within 3 mo after surgery	1 (2.00)	8 (6.00)	5.983	0.014
Chronic pelvic pain	2 (12.00)	12 (20.00)	8.306	0.004
Incision infection	0 (0.00)	3 (6.00)	3.093	0.079
Dysmenorrhea	5 (10.00)	11 (22.00)	2.679	0.102
Menstrual disorders	2 (4.00)	4 (8.00)	0.709	0.4
Intestinal obstruction	0 (0.00)	1 (2.00)	1.01	0.315

therapy is more likely to produce abdominopelvic adhesion[16]. Adhesions occur in 60% to 90% of gynaecological patients after abdominal pelvic surgery[17], and fibrous connections connecting tissue surfaces at abnormal locations can lead to chronic pelvic pain, infertility, intestinal obstruction, and the need for a complex reoperation[18-20]. In addition, it was found that in patients with long-term anti-infective therapy who underwent laparoscopic surgery, the abdominopelvic adhesion was more serious, the adhesion range was large, and the adhesion was dense, making it difficult to separate and a hindrance to surgery. The reason may be that 24-48 h after anti-infective therapy, the pelvic lesions are mainly composed of inflammatory exudate, and the membranoid adhesion is loose and easy to separate, which is more conducive to the surgery and thus to the postoperative effect. After 48-96 h of anti-infective therapy, inflammatory exudate on the surface of various organs of the patient's body can organize to form fibrin-like adhesion bands. Inflammatory exudates and tissue adhesions with increased density are hindrances to surgery and increase the incidence of postoperative complications. In addition, according to the above findings, we speculate that a smooth course of laparoscopic surgery and its increased efficacy after 24-48 h of anti-infective treatment may be related to the lower degree of psychological stress of patients before surgery. Ki *et al*[21] showed that compared with patients without anxiety before surgery, patients with anxiety before surgery had worse postoperative recovery quality. The researchers noted that anxiety before surgery can affect the quality of physical and mental recovery after surgery. In addition, Park *et al*[22] confirmed that anxiety and depression had a negative impact on the clinical outcome of rotator cuff repair. For the results of this study, we believe that a short period of anti-infection treatment before surgery can reduce the degree of psychological stress of patients before surgery and relieve anxiety and depression to promote a smooth operation and improve its curative effect. However, our views are limited to the research centre and the study population, thus it is necessary to expand the research scope to enhance the reliability of the results of this study.

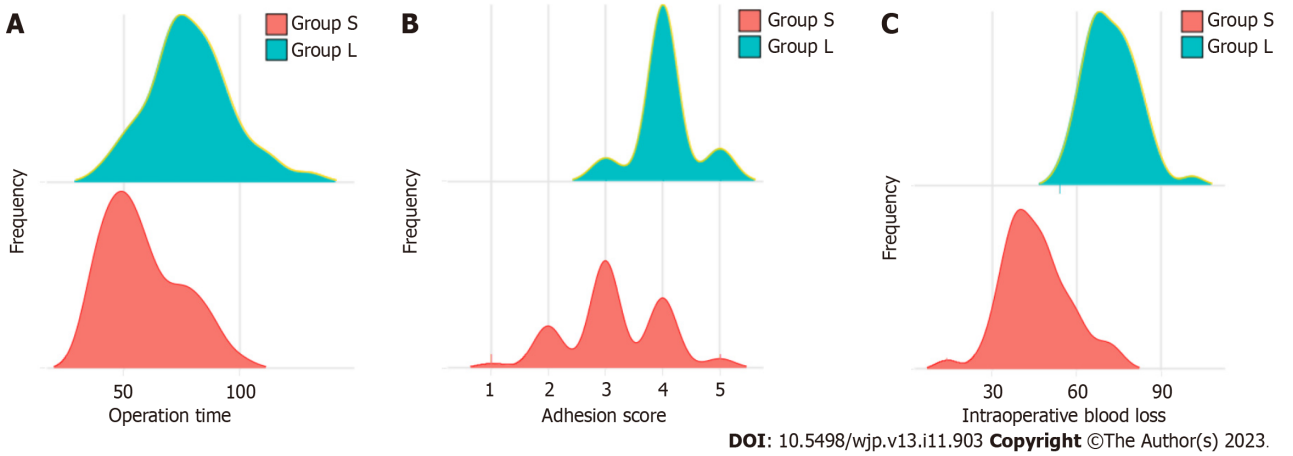
The data showed that in addition to pelvic pain and incision infection, there were complications such as injury to the surrounding organs in the Group S and the Group L after the surgery, and the incidence of dysmenorrhea was higher, which was mainly related to the difficulty of separation of a thick-walled abscess or the difficulty of removing inflammatory exudates on the surface of organs[23,24]. In addition, surgery may also be one of the reasons for a high incidence of complications. Laparoscopic operators should be aware of potential complications and how to prevent them, strictly adhere to the surgical indications during therapy and learn how to identify complications early to deal with them safely and effectively. In cases of difficult surgery, experienced surgeons are better suited to operate[25,26].

However, our study still has some limitations: (1) The patient data were collected from a single centre, making extrapolation difficult; (2) it is a retrospective study, and the results of our study can only offer recommendations, thus future prospective studies are needed to verify the research findings; and (3) The sample size was small, and there was considerable bias, so a large sample study is still needed to verify the conclusion.



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Figure 1 The difference in psychological stress. A: State anxiety score (SAS) before and after anti-infective therapy; B: Trait anxiety scores before and after anti-infective therapy; C: Self-rating anxiety scale scores before and after anti-infective therapy; D: Self-rating depression scale (SDS) scores before and after anti-infective therapy. Data are expressed as the mean ± SD. The state-trait anxiety score and SAS + SDS score of Group S were significantly lower than those of Group L after 24-48 h and 48-96 h of anti-infective therapy. S-AI: state anxiety; T-AI: trait anxiety; SAS: self-rating anxiety scale; SDS: self-rating depression scale. [a]*P* < 0.05, there is significant difference between group S and group L after anti-therapy.

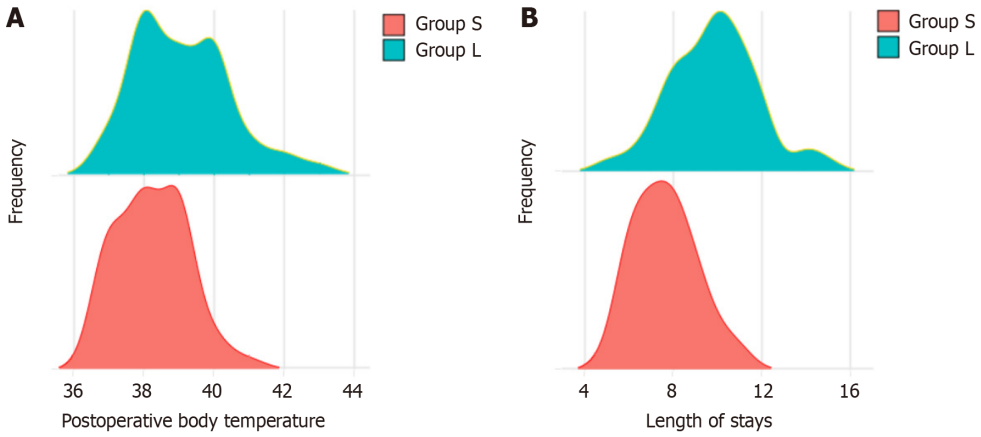


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Figure 2 Operation time, adhesion score, and intraoperative blood loss of the two groups. A: Operation time; B: Adhesion score; C: Intraoperative blood loss. The surgery time of Group S was shorter than that of Group L, and the adhesion score and intraoperative blood loss were lower than those of Group L (*P* < 0.05).

CONCLUSION

Compared with 48-92 h, 24-48 h of anti-infective therapy followed by laparoscopic surgery for pelvic abscesses is associated with less psychological stress in patients, is more conducive to surgery, and increases surgical efficacy.



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Figure 3 Postoperative body temperature and length of stay of the two groups. A: Postoperative body temperature; B: Length of stay. Postoperative body temperature was lower in Group S after 24-48 h of anti-infective therapy than in Group L after 48-96 h of anti-infective therapy ($P < 0.05$), and the hospital stay was shorter in Group S than in Group L ($P < 0.05$).

ARTICLE HIGHLIGHTS

Research background

Pelvic abscess is a serious pelvic inflammatory disease (PID). It can be caused by a variety of factors, including surgery (*e.g.*, low anterior resection), pelvic visceral perforation, diverticulitis, appendicitis, ischaemic colitis, inflammatory bowel disease, or PID.

Research motivation

Different durations of anti-infective therapy have different effects on patients' psychological state, the difficulty of laparoscopic surgery and surgical efficacy.

Research objectives

The aim of this study was to determine the optimal duration of preoperative anti-infective therapy in patients with pelvic abscesses.

Research methods

This study retrospectively analysed the differences in preoperative psychological stress, intraoperative operation difficulty and postoperative recovery of patients with pelvic abscesses after different durations of anti-infection treatment.

Research results

Among the 100 patients with pelvic abscesses, the patients who received 24-48 h of anti-infection treatment had less preoperative psychological stress, less intraoperative operation difficulty and better postoperative recovery than those who received 48-96 h of anti-infection treatment.

Research conclusions

Through observation, we put forward the theory that 24-48 h of anti-infection treatment is better than 48-96 h of anti-infection treatment for patients with pelvic abscesses undergoing laparoscopic surgery.

Research perspectives

The different effects of anti-infection treatment on patients' preoperative psychological stress and the difficulty and efficacy of laparoscopic surgery in patients with pelvic abscesses were observed.

FOOTNOTES

Author contributions: Zhang RR and Zhao RH conceived and designed the study; Zhang RR and Zhang L guided the study; Zhang RR and Zhao RH collected the clinical date; Zhang RR and Zhao RH analyzed the data; All authors drafted and revised the manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Suzhou Ninth Hospital affiliated to Soochow University (Suzhou Ninth People's Hospital).

Informed consent statement: All study participants or their legal guardians provided informed written consent prior to study enrolment.

Conflict-of-interest statement: All authors declare that there are no conflicts of interest.

Data sharing statement: The data for this study can be obtained from the corresponding author upon request.

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ORIGINAL ARTICLE

Retrospective Study

Correlation study between motor rehabilitation level and psychological state in patients with limb movement disorders after stroke

Xiao-Wan Li, Yu-Fu Xin, Ai-Hui Chang, Xiao-Ge Zhang, Yan Weng, Jia-Hao Yang, Qi-Zhi Fu

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Abstract

BACKGROUND

The psychological state of patients with post stroke limb movement disorders undergoes a series of changes that affect rehabilitation training and recovery of limb motor function.

AIM

To determine the correlation between motor rehabilitation and the psychological state of patients with limb movement disorders after stroke.

METHODS

Eighty patients with upper and lower limb dysfunction post stroke were retrospectively enrolled in our study. Based on Hospital Anxiety and Depression Scale (HADS) scores measured before rehabilitation, patients with HADS scores ≥ 8 were divided into the psychological group; otherwise, the patients were included in the normal group. Motor function and daily living abilities were compared between the normal and psychological groups. Correlations between the motor function and psychological status of patients, and between daily living ability and psychological status of patients were analyzed.

RESULTS

After 1, 2, and 3 wk of rehabilitation, both the Fugl-Meyer assessment and Barthel index scores improved compared to their respective baseline scores ($P < 0.05$). A greater degree of improvement was observed in the normal group compared to the psychological group ($P < 0.05$). There was a negative correlation between negative emotions and limb rehabilitation ($-0.592 \leq r \leq -0.233$, $P < 0.05$), and between negative emotions and daily living ability ($-0.395 \leq r \leq -0.199$, $P < 0.05$).

CONCLUSION

There is a strong correlation between motor rehabilitation and the psychological state of patients with post stroke limb movement disorders. The higher the negative emotions, the worse the rehabilitation effect.

Key Words: Stroke; Limb movement disorders; Motor rehabilitation; Psychological state; Correlation

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Core Tip: Stroke, also known as a cerebrovascular accident, is characterized by an acute and rapid onset and is the most common cerebrovascular disease. Stroke can cause limb dysfunction, resulting in functional limitations. Some people may experience a series of changes in their psychological state after illness, which affects rehabilitation training and recovery of limb function. The results of this study showed a strong correlation between the recovery of limb function with rehabilitation and psychological state of stroke patients. Therefore, it is necessary to pay close attention to psychological changes during rehabilitation, and implement timely adjustments and interventions for future rehabilitation.

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INTRODUCTION

Stroke can be subdivided into cerebral hemorrhage and cerebral infarction[1]. It is a clinical emergency that causes ischemic damage to the brain tissue due to the blockage or sudden rupture of small- and medium-sized blood vessels in the brain. According to the most recently published statistics, stroke ranks first as the leading cause of mortality in China, and is the main cause of accidental deaths, except for car accidents and falls from high altitudes[2]. Patients with stroke may experience swallowing and limb dysfunction, and in severe cases, they may lose their ability to take care of themselves, increasing the burden on their families and taking a serious negative toll on their mental health and resilience [3]. Therefore, it is necessary to pay close attention to psychological changes during rehabilitation, and implement timely adjustments and interventions for future rehabilitation and restoring the patient's quality of life.

The current medical disease model incorporates biological, psychological, and social factors. Medical workers should shift their treatment methods from traditional treatments to biological, psychological, and social models[4]. As the patient is anxious and worried when seeking medical treatment, the complex psychological effects can have pathogenic consequences[5]. Therefore, we should pay attention to the patients' psychological states, carefully observe their psychological reactions, and implement targeted psychological interventions based on their characteristics[6]. Related studies have shown that psychological interventions can reduce anxiety, depression, and fear in patients by reducing the heart rate, blood pressure, and catecholamine levels in blood and urine, and alleviate tension during exercise[7]. It can inhibit the activity of nociceptive neurons in the central area of the cerebral cortex, reduce their excitability, increase the pain threshold, and alleviate pain[8].

According to previous reports, there is a correlation between recovery and psychological state of the patient[9]. The better the patient's psychological state, the better will be their limb function recovery, and their quality of life will also improve accordingly[10]. This article mainly studied the correlation between the recovery of limb function owing to rehabilitation and psychological resilience in elderly stroke patients to provide a reference for psychological nursing and quality of life intervention in elderly stroke patients.

MATERIALS AND METHODS

Patient characteristics

Eighty patients with limb dysfunction after stroke who were admitted to the First Affiliated Hospital of Henan University of Science and Technology from May 2022 and May 2023 were retrospectively selected. The inclusion criteria were as follows: (1) A confirmed diagnosis of stroke on head computed tomography or magnetic resonance imaging according to

the diagnostic criteria proposed by the American Heart Association/American Stroke Association for stroke[11]; (2) The course of treatment is more than 21 d, and the condition is stable without recurrence; (3) The patient has a clear sense of autonomy and good cognitive ability; and (4) Patients with limb dysfunction after stroke. The exclusion criteria included: (1) Other serious cardiovascular and cerebrovascular diseases; (2) Patients with malignant tumors; (3) Patients with mental illness; (4) Patients with unstable vital signs; (5) Patients with previous stroke but residual upper and lower limb dysfunction and other sequelae; and (6) Patients with a history of surgery, fractures, arthritis, or pain that affects the recovery of upper and lower limb function. Based on the Hospital Anxiety and Depression Scale (HADS) scores before the start of rehabilitation, the patients were divided into the psychological group (those with HADS scores ≥ 8) and the normal group (those with HADS scores < 8).

Evaluation indices

The HADS index was used to evaluate the psychological state of patients[12]. This is a 14-item scale with seven items rated as anxiety and seven items rated as depression. If the HADS score is ≥ 8, it indicates symptoms of anxiety and depression. If the HADS score is < 8, the patient's psychological state is considered normal.

The Fugl-Meyer assessment (FMA) was used to evaluate the patient's upper and lower limb motor function[13]. There were 50 items with a total maximum score of 100 points. The upper limb score consists of 33 items and 66 points. The lower upper limb score consists of 17 items and with a total of 34 points.

The Barthel index (BI) for activities of daily living[14] was used to assess the patients' daily living abilities. The BI includes 10 items, with a total of 100 points. Except for walking on flat ground and bed-to-chair transfer, the full score was 15 points, whereas the full score for grooming and bathing was 5 points. The remaining items had a total score of 10 points.

Statistical analysis

SPSS 20.0 was used to statistically analyze the data. The measurement data were represented by (mean ± SD), and the *t*-test was used for intergroup comparisons. The counting data is represented in the form of percentage, and χ^2 is used for the intergroup comparisons. Pearson's correlation analysis was used to analyze the relationship between the rehabilitation of limb function and the psychological status of patients as well as the relationship between daily living ability and psychological status. Statistical significance was set at $P < 0.05$.

RESULTS

The comparison of general data

As shown in Table 1, there were no differences between gender (male, 60% *vs* 62.5%), age (65.33 ± 4.59 *vs* 65.90 ± 4.91), body mass index (25.43 ± 2.08 *vs* 25.86 ± 1.74), and course of disease (27.93 ± 7.11 *vs* 27.83 ± 7.88) between the normal and psychological groups ($P > 0.05$). The results showed that most stroke patients with motor disorders were classified as elderly and the duration of the disease was between 1 and 2 mo.

The comparison of motor function between normal and psychological groups

As shown in Figures 1A and B, there was no difference in the FMA scores of the upper and lower limbs between the normal and psychological groups ($P > 0.05$). After 1, 2, and 3 wk of rehabilitation, the FMA scores of the upper and lower limbs improved in both groups ($P < 0.05$). In addition, the FMA scores of the upper and lower limbs in the normal group had more substantial improvement than those in the psychological group ($P < 0.05$).

The comparison of daily living ability between the normal and psychological group

Figure 1C shows that before rehabilitation, there was no difference in the BI scores between the normal and psychological groups ($P > 0.05$). After 1, 2, and 3 wk of rehabilitation, the BI score improved in both groups ($P < 0.05$), and the BI score in the normal group was higher than that in the psychological group ($P < 0.05$).

The correlation between negative emotions and limb rehabilitation

As shown in Table 2, there was a negative correlation between anxiety and upper, lower limb FMA scores at 1-, 2- and 3-wk post rehabilitation ($P < 0.05$). There was a negative correlation between depression and upper, lower limb FMA scores at 1-, 2- and 3-wk post rehabilitation ($P < 0.05$). These results suggested a negative correlation between negative emotions and limb rehabilitation.

The correlation between negative emotions and daily living ability

There was a negative correlation between anxiety and BI scores at 2- and 3-wk post rehabilitation ($P < 0.05$), and there was a negative correlation between depression and BI scores at 1-, 2- and 3-wk post rehabilitation ($P < 0.05$) (Table 3). These results suggest a negative correlation between negative emotions and activities of daily living.

Table 1 The comparison of general data between normal and psychological groups

Index	Normal group (n = 40)	Psychological group (n = 40)	t/χ^2	P value
Gender (male, %)	24 (60%)	25 (62.5%)	-0.053	0.818
Age (yr)	65.33 ± 4.59	65.90 ± 4.91	-0.541	0.590
BMI (kg/m^2)	25.43 ± 2.08	25.86 ± 1.74	-0.997	0.322
Course of disease (d)	27.93 ± 7.11	27.83 ± 7.88	0.060	0.953

BMI: Body mass index.

Table 2 The correlation between emotions and limb rehabilitation

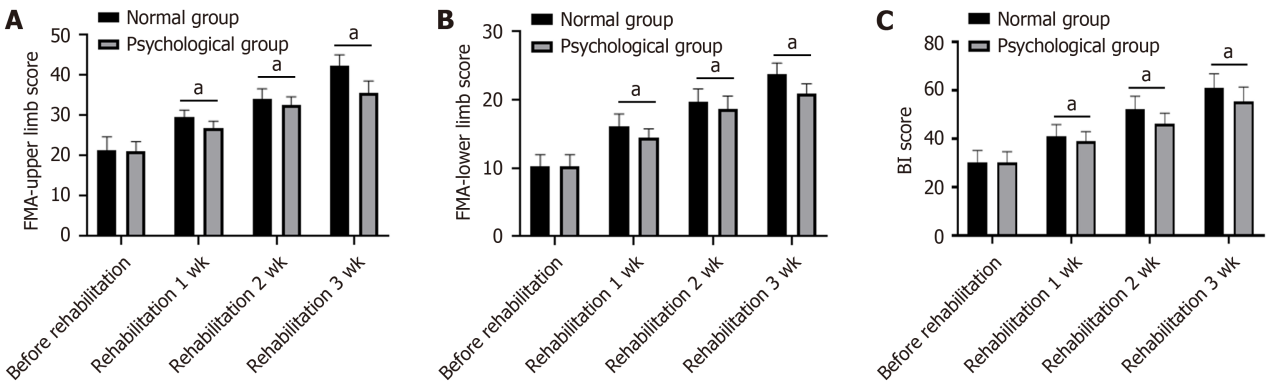
	FMA score of upper limb			FMA score of lower limb		
	1 wk	2 wk	3 wk	1 wk	2 wk	3 wk
Anxiety	r = -0.341	r = -0.339	r = -0.592	r = -0.288	r = -0.289	r = -0.454
	P = 0.005	P = 0.002	P < 0.001	P = 0.010	P = 0.009	P < 0.001
Depression	r = -0.319	r = -0.233	r = -0.585	r = -0.369	r = -0.255	r = -0.475
	P = 0.012	P = 0.038	P < 0.001	P = 0.001	P = 0.023	P < 0.001

FMA: Fugl-Meyer assessment.

Table 3 The correlation between emotions and daily living ability

	BI score		
	1 wk	2 wk	3 wk
Anxiety	r = -0.199	r = -0.377	r = -0.395
	P = 0.077	P = 0.001	P < 0.001
Depression	r = -0.233	r = -0.379	r = -0.387
	P = 0.038	P = 0.001	P < 0.001

BI: Barthel index.



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Figure 1 The comparison of motor function and daily living ability between normal and psychological groups. A: Fugl-Meyer assessment (FMA)-upper limb score; B: FMA-lower limb score; C: Daily living ability. FMA: Fugl-Meyer assessment. BI: Barthel index. ^aP < 0.05.

DISCUSSION

The incidence of cerebrovascular diseases and stroke, which is the most common type of cerebrovascular disease[15], has increased annually, and they generally occur in the younger and middle-aged group[16]. Once affected by stroke, patients with mild disease may experience delayed movement, whereas those with severe disease phenotypes may experience limb dysfunction and even death. Some people may experience a series of changes in their psychological state after illness, which affects rehabilitation training and recovery of limb function[17]. Elderly people have decreased bodily functions, more comorbidities, and a strong psychological dependence on their families[18]. After a period of illness, they not only have to endure the torment of illness but also the inconveniences of life. These patients bear significant psychological pressure as a result.

Many patients find it difficult to complete role conversion in a short time; the rehabilitation training initiative is poor, the effect is not obvious, depression and pessimism appear, psychological resilience becomes affected, and it is easily complicated with acute stress disorder; that is, some separation symptoms, such as mental, movement, and personality dysfunction appear in the early stages of the illness[19]. Those with avoidance and high vigilance towards illness events deliberately avoid the facts about one's own illness, suspect the gaze of others, are unable to control one's emotions and temper, and are prone to irritability, anger, and poor sleep quality[20].

This study used the HADS to evaluate the psychological status of patients with limb movement disorders after stroke and to determine whether they had anxiety and depression before rehabilitation initiation. In previous studies that followed-up stroke patients, it was hypothesized that fear of pain affects post-stroke functional recovery; however, there was no correlation between the two[21]. It is recommended that patients pay attention to their fears and receive reasonable psychological interventions. Related studies suggest that anxiety and depression affect the recovery of limb function in stroke patients[22]. Our study showed that the motor function and daily living ability of stroke patients in the psychological group were lower than those in the normal group after 1-, 2-, and 3-wk of rehabilitation, indicating that anxiety and depression negatively impact the recovery of motor function and daily living ability. Further, our research showed a significant negative correlation between negative emotions such as anxiety and depression, motor function, and self-life ability. This was because patients in the psychological group had a poor psychological state and lacked the ability to withstand stress[23]. They are unable to establish a good buffer time after the illness, which is not conducive to the creation of positive emotions and is even less conducive to the recovery of upper and lower limb function after stroke[24].

Therefore, we should attach importance to the psychological state of patients before rehabilitation, and it is recommended that future studies address the following points to achieve better outcomes: Firstly, rehabilitation plans should be developed to improve patients' quality of life, take effective psychological intervention measures, and observe and evaluate the actual effects. This may be done by equipping dedicated psychologists with the correct resources to strengthen research on the psychological status of stroke patients before rehabilitation. Secondly, optimal treatment methods should be adopted to reduce and eliminate the adverse effects of psychological factors on limb motor function before rehabilitation. Furthermore, attention should be paid to the psychological rehabilitation of patients after discharge and to strengthen follow-up procedures. Finally, the active cooperation between psychologists and rehabilitation physicians must be strengthened to minimize negative psychological impacts.

Our study has several limitations. There are many factors that affect the recovery of limb motor function, and psychological factors are only one of them. This study only considered the effects of anxiety and depression on limb motor function recovery before rehabilitation. Further research is needed to investigate the effects of other factors on recovery of limb motor function. The evaluation of various indices in this study are mostly in the form of a subjective numeric rating scale. At the same time, due to differences in language expression and understanding among ethnic minorities, there may have been errors in the measurement of each indicator. In the future, more objective indicators such as imaging findings should be used to quantify the results more accurately. This study only examined the impact of psychological factors before rehabilitation on limb motor function rehabilitation, without considering the impact of psychological factors, and it did not consider effective psychological intervention measures for adverse psychological outcomes. This must be investigated in the future. Finally, sample size of this study was small, and future multi-center studies with larger sample sizes are needed to confirm this finding.

CONCLUSION

In summary, there is a certain correlation between the psychological state of patients with limb disorders after stroke and their level of limb rehabilitation; the greater the negative emotions, the worse the rehabilitation effect. In clinical practice, healthcare workers can assist in the rehabilitation of patients' limb functions by improving their psychological state, indirectly improving their quality of life.

ARTICLE HIGHLIGHTS

Research background

The rehabilitation of limb function in patients with limb movement disorders after stroke is influenced by their psychological state.

Research motivation
Exploring whether healthcare workers can accelerate the recovery of limb function in stroke patients by improving their psychological state and indirectly improving their quality of life.

Research objectives
The aim of this study was to investigate the correlation between the level of motor rehabilitation and the psychological state of patients with limb movement disorders post stroke.

Research methods
Eighty patients with limb dysfunction after stroke were retrospectively selected. The Fugl-Meyer assessment motor function and Barthel index daily living ability scales were used to investigate limb movement disorders and daily living ability, and a correlation between the two indices and psychological state was observed.

Research results
There was a negative correlation between negative emotions and limb rehabilitation and between negative emotions and daily living ability.

Research conclusions
The better the psychological state of patients with limb movement disorders after stroke, the more significant the rehabilitation effect on limb function recovery.

Research perspectives
When performing limb function rehabilitation in patients with limb movement disorders after stroke, it is necessary to pay attention to the patient's psychological state. A good psychological state can accelerate recovery.

FOOTNOTES

Author contributions: Li XW designed the study and wrote the paper; Fu QZ designed the study and supervised the report; Xin YF organized and analyzed the data; Zhang XG and Weng Y provided clinical advice; Chang AH and Yang JH organized the references.

Institutional review board statement: The study was reviewed and approved by the First Affiliated Hospital of Henan University of Science and Technology (Approval No. 2022-03-B160).

Informed consent statement: This study used only anonymous patient data and exempted the requirement for informed consent according to policy.

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ORIGINAL ARTICLE

Observational Study

Relationship between primary caregivers' social support function, anxiety, and depression after interventional therapy for acute myocardial infarction patients

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Abstract

BACKGROUND

An acute myocardial infarction (AMI) is often treated with direct coronary intervention and requires home-based rehabilitation. Caregivers of patients with AMI need adequate social support to maintain high-quality care; however, their social support function is low, and relevant indicators for intervention must be identified.

AIM

To analyze the correlation between social support for primary caregivers, their anxiety, and depression, when caring for patients with AMI after interventional therapy.

METHODS

Using convenience sampling, we selected 300 primary caregivers of patients with AMI who had undergone interventional therapy. The Social Support Rating Scale (SSRS), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS) were used to assess the primary caregivers. A Pearson's correlation analysis was used to analyze the correlations between the SSRS, SAS, and SDS, and a multiple logistic regression analysis was used to analyze the factors influencing the low social support function of primary caregivers. The receiver operating characteristic curve and area under the curve (AUC) were used to evaluate the predictive ability of the SAS and SDS for low social support function in primary caregivers.

RESULTS

Considering the norm among Chinese people, AMI caregivers' objective support, subjective support, support utilization, and SSRS scores were lower, while their SAS and SDS scores were higher. The SSRS scores of female caregivers were higher than those of the male caregivers (t = 2.123, P = 0.035). The Pearson correlation analysis showed that objective support, subjective support, support utilization, and SSRS total scores were significantly correlated with both SAS (r = -0.414, -0.460, -0.416, -0.535) and SDS scores (r = -0.463, -0.379, -0.349, -0.472). Among the 300 AMI caregivers, 56 cases (18.67%) had a low level of support function (SSRS ≤ 22 points). Logistic regression model analysis showed that SAS and SDS were independent risk factors for low social support function of AMI caregivers, regardless of adjustment for other variables (P < 0.05). SAS and SDS predicted that the AUC of AMI caregivers with low support function was 0.84, sensitivity was 67.9 and 71.4, and specificity was 84.0 and 70.9, respectively.

CONCLUSION

The social support function of the primary caregiver of patients with AMI after interventional therapy was lower and negatively correlated with anxiety and depression in the primary caregiver.

Key Words: Acute myocardial infarction; Primary caregivers; Social support function; Anxiety; Depression; Relationship

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Core Tip: High levels of social support help caregivers implement care. Intervention in the social support function of the primary caregiver is beneficial for the postoperative recovery of patients with acute myocardial infarction (AMI) after interventional therapy. To find a new intervention direction, we proposed a relationship between the social support function of primary caregivers of patients with AMI, and anxiety and depression; this is a breakthrough in improving the social support function of primary caregivers.

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INTRODUCTION

Acute myocardial infarction (AMI) is myocardial necrosis caused by acute or persistent ischemia and hypoxia in the coronary arteries. It is typically characterized by persistent chest pain[1]. Usually, after rest and use of nitrates, patients do not receive complete relief but experience arrhythmia, shock, or heart failure, resulting in loss of daily living ability and serious mental and behavioral disorders. According to relevant surveys and research data, the incidence of AMI in China has increased sharply in recent years, with the average annual number of new cases exceeding 500000[2]. Acute ST-elevation myocardial infarction (STEMI) within 12 h is usually treated with direct coronary intervention[3]. Postoperatively, most patients require home-based rehabilitation and caregiver care. During rehabilitation, the physical and mental state of the caregiver affects the prognosis and degree of recovery of the patient. The patient's condition also affects the physical and psychological states, as well as the quality of the caregiver's life, thus affecting their ability and quality of care[4]. Caregivers experience physical and emotional stress during the long-term care process. As a relative of the patient, the caregiver experiences heavy emotional stress and shoulders financial pressure. Studies have found that if caregivers receive sufficient social support, they can maintain their physical and mental health better and adapt to their caregiving role[5]. Ensuring a high social support function for caregivers has a positive clinical significance for patients' rehabilitation. However, there is a lack of effective intervention strategies to improve caregivers' social support, and more clinical evidence is needed to support the factors related to social support. Research has found that caregivers of patients with AMI often have different negative emotional levels of anxiety and depression[6,7]. Therefore, we propose that the social support function of caregivers of patients with AMI may be related to anxiety and depression. Based on this, we selected 300 primary caregivers of patients undergoing interventional treatment for AMI.

Considering the above, this study aims to investigate the levels of social support, anxiety, and depression among caregivers of AMI patients, and analyze the correlation between the social support function of main caregivers and their anxiety and depression after interventional therapy, to provide a reference for improving the quality of home care.

MATERIALS AND METHODS

Source of research object

Using convenience sampling, we selected 300 primary caregivers of patients with AMI who received concurrent interventional treatment at the Affiliated Hospital of Jiangnan University, between January 2021 and December 2022.

Patients needed to comply with the following conditions: (1) Show AMI symptoms and evidence of myocardial ischemia[8]; (2) Be diagnosed with acute STEMI within 12 h and treated with coronary intervention; and (3) Be 18 years or older. The caregiver was required to meet the following conditions: (1) Be at least 18 years of age; (2) Be the patient's immediate family member and has been caring for the patient for the longest time (*i.e.*, is the patient's primary caregiver); (3) Have normal reading and writing ability and be able to complete the questionnaire independently; and (4) Be aware of this research and voluntarily agree to be investigated. The caregiver could not have the following conditions: (1) Mental abnormalities or intellectual disabilities; (2) Language expression and communication barriers; (3) A history of alcohol or drug dependence; or (4) Be a paid caregiver.

Survey tool

General information questionnaire. Based on a literature review and expert consultation, a general information questionnaire was prepared, which included age, gender, number of hospitalizations, payment method of medical expenses, proportion of out-of-pocket medical expenses to family income, course of the disease, heart function, and daily living ability. Caregivers' general information included age, gender, education level, marital status, relationship with patients, monthly family income, caretaking experience, number of other caregivers, *etc.*, as well as the age of patients, time from onset to admission, and Killip grade.

The Social Support Rating Scale (SSRS)[9] was created by domestic scholar Xiao Shui-Yuan in 1986, to assess the status of people's social support, including subjective support, objective support, and support utilization. The scale comprises three dimensions and ten items, with the total score being the sum of the scores for each item. Higher scores indicate higher levels of social support. The total score is 66 points, of which ≤ 22 points are rated as low level, 23–44 points as medium, and 45–66 points as high. The retest reliability is 0.92, and the reliability and validity of all items are high (Cronbach's α coefficient was 0.89–0.94). The SSRS Chinese norm refers to the work of Zhang *et al*[10], in which a norm established based on the population of the whole country as a sampling population. This is the reference value.

The Self-Rating Anxiety Scale (SAS)[11], developed by Zung in 1971, was used to assess the subjective feelings of patients with anxiety. The scale contains 20 items and the score criteria are as follows: 1 point for no or very little time; 2 points for a small amount of time; 3 points for more time; and 4 points for most of the time. The scores were added together to obtain a rough score, and multiplied by 1.25 to obtain a standard score. The higher the score, the greater the anxiety. The Cronbach's α coefficient of the scale was 0.931.

The Self-Rating Depression Scale (SDS)[12] developed by Zung in 1965 was used to assess the subjective feelings of patients with depression, with a total of 20 items. The scoring criteria for each item were as follows: Occasionally, 1 point; sometimes, 2 points; often, 3 points; and always, 4 points. The total score is rough, and the gross score multiplied by 1.25 equals the standard score. Higher scores indicate more severe depression. The Cronbach's α coefficient of the scale was 0.927. Both SAS and SDS Chinese norms refer to the literature of Kang[13], which provides a norm based on the population of the whole country as a sampling population, and has reference value.

Investigation method

Community doctors or nurses with uniform training conducted household surveys with primary caregivers or invited them to community health service institutions to complete the surveys. The researcher informed the primary caregivers of the purpose, significance, and participation method of the survey and encouraged them to provide their informed consent, which was explained to them in simple and understandable language. Subsequently, the primary caregivers completed the questionnaire. The researchers assisted those with low cultural or language abilities in completing the questionnaires. Questionnaires were completed with confidential information and collected immediately. A total of 329 questionnaires were sent out; 306 questionnaires were returned, and 300 effective questionnaires were obtained; an effective rate of 98.04%.

Quality control

To reduce the risk of privacy disclosure, the respondents were surveyed anonymously. We arranged the questionnaire survey in an independent room, allowed the investigator and primary caregiver to be present during the investigation, and entered the data through double cross-entry and cross-examination.

Statistical analysis

SPSS (version 23.0) was used for the data analysis and processing. Case numbers described counting data; mean ± standard deviation describes measurement data tested by a line test or an F-test; a Pearson's correlation was used to analyze correlation, a multiple linear regression explored risk factors, and receiver operator characteristic curve (ROC) and area under the curve (AUC) predicted ability evaluation; Test level: $\alpha = 0.05$.

Table 1 Comparison of Social Support Rating scale scores of primary caregivers with Chinese norms

SSRS items	SSRS score (*n* = 300)	Chinese norm (*n* = 3342)	*t* value	*P* value
Objective support	7.05 ± 1.6	9.1 ± 3.0	11.690	< 0.001
Subjective support	16.9 ± 5.0	23.5 ± 4.3	25.110	< 0.001
Support utilization	4.7 ± 1.3	7.8 ± 2.0	26.350	< 0.001
Total scores of AMI caregivers	28.56 ± 5.31	40.5 ± 2.8	64.230	< 0.001

SSRS: Social Support Rating scale; AMI: Acute Myocardial Infarction.

Table 2 Comparison of Self Rating Anxiety Scale scores and SDS scores of primary caregivers with Chinese norms

Items	Scores (*n* = 300)	Chinese norm (*n* = 1338)	*t* value	*P* value
SAS	41.26 ± 6.58	29.78 ± 10.07	18.860	< 0.001
SDS	44.16 ± 7.54	33.46 ± 8.55	20.000	< 0.001

SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale.

RESULTS

Primary caregivers had low SSRS

Compared with the Chinese norm, the objective support, subjective support, support utilization, and total scores of AMI caregivers were lower ($P < 0.05$) (Table 1).

The SAS and SDS scores of primary caregivers were higher

Compared with the Chinese norm, the scores of SAS and SDS among caregivers of patients with AMI were higher ($P < 0.05$) (Table 2).

SSRS scores of primary caregivers with different characteristics

There were no differences in the SSRS scores among different age groups, gender, education level, marital status, relationship with patients, monthly family income, caregiving experience, number of other caregivers, age of patients, time from onset to admission, or Killip rating of patients ($P > 0.05$); however, the SSRS scores of female caregivers were higher than those of male caregivers ($P < 0.05$) (Table 3).

Correlation between the SSRS score and SAS score or SDS score

Through the Pearson correlation analysis, objective support, subjective support, support utilization, and total SSRS scores were found to be negatively correlated with SAS (r = -0.414, -0.460, -0.416, -0.535, respectively) and SDS scores (r = -0.463, -0.379, -0.349, -0.472, respectively) ($P < 0.05$) (Table 4).

Multiple regression analysis affecting primary caregiver support function

Among the 300 AMI caregivers, 56 cases (18.67%) had a low level of support function (SSRS ≤ 22 points). We used the support function (1 = low level, 0 = medium-high level) as the dependent variable and the characteristic indicators as self-variables (assigned values are shown in Table 5) of the logistic regression model analysis. SAS and SDS were independent determinants of low support function among AMI caregivers, regardless of adjustment for other variables ($P < 0.05$) (Table 6).

The ability of SAS and SDS scores to predict low social support function in AMI caregivers

The AUC of the SAS and SDS for predicting AMI caregivers with low social support function was 0.84, sensitivity was 67.9 and 71.4, and specificity was 84.0 and 70.9, respectively (Table 7 and Figure 1).

DISCUSSION

At present, the mental health outlook of family caregivers of patients with AMI in China is not optimistic, which directly affects their caring ability. The poor caring ability of caregivers not only affects the condition and prognosis of patients with AMI but also affects their physical and mental health. Therefore, it is necessary to explore the relationship between the social support function of primary caregivers, their anxiety, and their depression.

Table 3 Social Support Rating Scale scores of primary caregivers with different characteristics

Characteristics	Cases	SSRS scores	*t/F* value	*P* value
Age			1.317	0.189
< 60 yr	229	29.47 ± 6.96		
≥ 60 yr	71	28.25 ± 6.34		
Gender			2.123	0.035
Female	172	29.47 ± 6.96		
Male	128	27.89 ± 5.49		
Education levels			1.172	0.311
Junior high school and below	83	28.96 ± 7.16		
High school or technical secondary school	100	30.07 ± 6.24		
College or above	117	28.71 ± 6.98		
Marital status			3.382	3.382
Never married	80	28.44 ± 8.03		
Married	153	27.42 ± 5.45		
Divorced or widowed	67	29.84 ± 6.25		
Relationship with patients			0.8741	0.874
Mate	105	27.98 ± 5.67		
Parent	98	27.76 ± 6.70		
Sons and daughters	65	29.09 ± 7.09		
Other	32	29.28 ± 7.11		
Monthly family income			0.607	0.546
< 5000 RMB	96	28.72 ± 6.85		
5000–10000 RMB	128	27.95 ± 5.39		
> 10000 RMB	76	28.79 ± 6.76		
Caregiving experience			0.149	0.882
No	202	29.29 ± 7.46		
Yes	98	29.16 ± 6.30		
Number of other caregivers			1.036	1.036
0	55	29.62 ± 6.15		
1 or 2	157	28.65 ± 7.003		
≥ 3	88	27.95 ± 6.67		
Age of patients			0.571	0.568
< 60 yr	221	28.63 ± 7.42		
≥ 60 yr	79	29.17 ± 6.59		
Time from onset to admission			0.683	0.495
< 10 h	114	29.21 ± 6.64		
≥ 10 h	186	28.64 ± 7.23		
Killip rating of patients			1.065	0.288
Level 1 or 2	221	28.82 ± 7.15		
Level 3 or 4	79	27.84 ± 6.64		

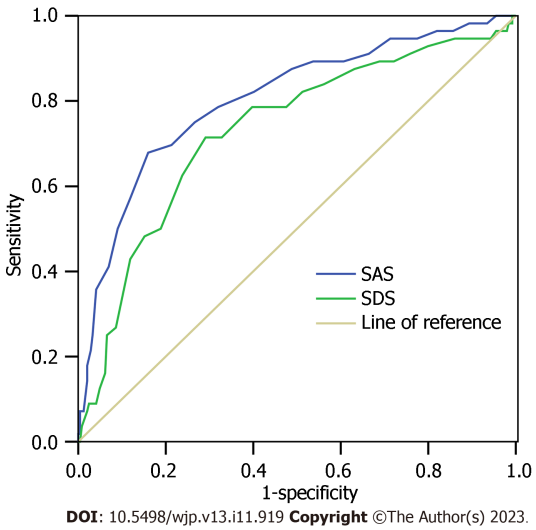
Table 4 Correlation between Social Support Rating Scale score, Self Rating Anxiety Scale score, and Self Rating Depression Scale score

SSRS items	SAS score		SDS score	
	r value	*P* value	*r* value	*P* value
Objective support	-0.414	< 0.001	-0.463	< 0.001
Subjective support	-0.460	< 0.001	-0.379	< 0.001
Support utilization	-0.416	< 0.001	-0.349	< 0.001
Total SSRS score	-0.535	< 0.001	-0.472	< 0.001

SSRS: Social Support Rating Scale; SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale.

Table 5 Assignment

Independent variable	Assignment
Age	0 = < 60 yr, 1 = ≥ 60 yr
Gender	0 = female, 1 = male
Education levels	0 = junior high school and below, 1 = high school or technical secondary school, 2 = college or above
Marital status	0 = spinsterhood, 1 = married, 2 = divorced or widowed
Relationship with patients	0 = mate, 1 = parent, 2 = sons and daughters, 3 = other
Monthly family income	0 = < 5000 RMB, 1 = 5000–10000 RMB, 2 = > 10000 RMB
Caregiving experience	0 = no, 1 = yeas
Number of other caregivers	0 = 0, 1 = 1 or 2, 2 = ≥ 3
Age of patients	0 = < 60 yr, 1 = ≥ 60 yr
Time from onset to admission	0 = < 10 h, 1 = ≥ 10 h
Killip rating of patients	0 = level 1 or 2, 1 = level 3 or 2



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Figure 1 Receiver operator characteristic curve analysis of Self-Rating Anxiety Scale score and Self-Rating Depression Scale score prediction. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

Table 6 Multiple regression analysis affecting primary caregiver support function

Independent variable	B	SE	Wals	*P* value	OR	95% CI	
						Lower limit	Upper limit
No other variables were adjusted							
SAS	0.177	0.032	30.813	< 0.001	1.194	1.121	1.271
SDS	0.070	0.026	7.288	0.007	1.072	1.019	1.128
Constant	-12.392	1.723	51.741	< 0.001	< 0.001		
After adjusting for other variables							
SAS	0.193	0.035	30.566	< 0.001	1.213	1.133	1.300
SDS	0.068	0.028	6.008	0.014	1.071	1.014	1.131
Age	-0.261	0.488	0.287	0.592	0.770	0.296	2.003
Gender	0.133	0.395	0.113	0.737	1.142	0.527	2.477
Education levels			0.550	0.760			
High school or technical secondary school	0.298	0.452	0.434	0.510	1.347	0.555	3.269
College or above	-0.044	0.449	0.010	0.922	0.957	0.397	2.306
Marital status			0.140	0.932			
Married	0.091	0.535	0.029	0.864	1.096	0.384	3.127
Divorced or widowed	-0.073	0.462	0.025	0.875	0.930	0.376	2.298
Relationship with patients			1.974	0.578			
Parent	0.253	0.694	0.133	0.715	1.288	0.331	5.019
Sons and daughters	0.759	0.699	1.179	0.278	2.135	0.543	8.400
Other	0.339	0.728	0.217	0.641	1.404	0.337	5.848
Monthly family income			3.042	0.218			
5000–10000 RMB	0.453	0.462	0.960	0.327	1.573	0.636	3.893
> 10000 RMB	-0.281	0.519	0.293	0.588	0.755	0.273	2.087
Caregiving experience	-0.294	0.399	0.540	0.462	0.746	0.341	1.631
Number of other caregivers			1.015	0.602			
1 or 2	0.351	0.552	0.406	0.524	1.421	0.482	4.188
≥ 3	0.416	0.418	0.991	0.320	1.515	0.668	3.435
Age of patients	-0.051	0.439	0.013	0.908	0.950	0.402	2.249
Time from onset to admission	-0.008	0.385	0.000	0.983	0.992	0.467	2.108
Killip rating of patients	-0.172	0.424	0.164	0.685	0.842	0.367	1.933
Constant	-13.699	2.070	43.780	< 0.001	< 0.001	–	–

SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale; B: Regression Coefficient β; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.

Table 7 Self Rating Anxiety Scale scores and Self Rating Depression Scale scores predicted the area under the curve of primary caregivers with low levels of social support

Test result variable	AUC	SE	*P* value	95%CI	Sensitivity (%)	Specificity (%)	Optimum cutoff value
SAS	0.84	0.84	< 0.001	0.737, 0.872	67.9	84.0	45.5
SDS	0.84	0.84	< 0.001	0.655, 0.807	71.4	70.9	47.5

SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale; AUC: Area under the curve; CI: Confidence interval.

The occurrence of AMI affects not only patients, but also their families and caregivers[14]. Compared with the norms in China, caregivers' objective support, subjective support, support utilization, and total SSRS scores were lower, while the SAS and SDS scores were higher. This indicates that the social support function of primary caregivers was generally low, and that negative emotions of anxiety and depression were more common, which should be considered. These results confirm those of previous studies[15,16]. The social support function of primary caregivers was generally low, which may be due to an imperfect medical security system and deficiencies in follow-up and community nursing, resulting in less social support for primary caregivers. Additionally, problems such as drug side effects and social discrimination can indirectly lead to primary caregivers' self-isolation and reluctance to seek outside help, thereby greatly reducing the availability of social support. Good social support stems from the need for spiritual comfort and support from family, friends, and community. This situation serves as a warning to medical staff to pay attention to social support, assist primary caregivers in establishing social support systems, and enhance their social support functions.

Anxiety is defined as an inner restlessness and fear with no obvious objective causes, whereas depression is defined as persistent low mood in terms of clinical characteristics of the state of mind. The long-term care of patients with AMI undergoing interventional surgery negatively affects the mental health of their primary caregivers. Because AMI is often associated with varying degrees of dysfunction after surgery, the primary caregiver must provide frequent in-bed turning and back-patting to prevent bedsores and transfer patients between beds and wheelchairs. The primary caregiver takes care of the patient in various aspects, such as daily activities, daily living, and diet, and expends a lot of physical strength, time, and energy, which is extremely costly for the body and mind of the primary caregiver and must be maintained for a long time. Primary caregivers also face personality changes in patients with AMI, which will produce psychological reactions such as helplessness, depression, anger, loneliness, and boredom during the care process, affecting normal emotional functions. Patients who have not fully recovered after surgery may relapse[17]; moreover, their primary caregivers must consider both the patient's condition and the financial burden it brings. Such repeated worries aggravate anxiety and depression.

Social support refers to the help people receive from society or others through their social networks; it includes objective support, subjective support, and support utilization. According to the results of our Pearson's correlation analysis, objective support, subjective support, support utilization, and total SSRS scores were significantly negatively correlated with SAS and SDS scores, suggesting that with the increase in anxiety and depression among primary caregivers of patients with AMI, their social support function is lower, which is consistent with some existing research results[18,19]. Further, our multiple linear regression analysis found that the SAS score [odds ratio (OR) = 1.194] and SDS score (OR = 1.072) were independent influencing factors of low social support function in primary caregivers; these two indicators could accurately predict the risk of low social support, and the sensitivity and specificity of the prediction reached more than 65%. The results showed that, after excluding other interfering factors, the lower the anxiety and depression experienced by the primary caregiver, the stronger the social support function. A possible explanation for this effect is that the lower the social support function of the primary caregiver, the greater the caring burden[20], and the more likely it is to produce anxiety and depression. Research also shows that good social support can not only promote the physical health of caregivers, but also effectively relieve their depression and anxiety[13]. According to research by the Chinese Academy of Social Sciences, social support can not only improve the psychological satisfaction of the body, but also alleviate its negative emotions[21]. Therefore, the community should not only pay attention to the primary caregivers of AMI patients undergoing interventional surgery, but should also strengthen the care and help of caregivers by providing adequate psychological support and encouragement. Family visits, caregiver experience exchange platforms, rehabilitation guidance, and other measures can reduce the burden on caregivers, improve the mental health of caregivers and patients, and achieve a win–win outcome.

The limitations of this study is that it is a single-center study, and the results can only reflect part of the population; therefore, whether it can be generalized to the general population is unknown. Further, the inclusion of characteristic indicators of primary caregivers is limited, meaning that potential impact indicators may have been overlooked. Therefore, future studies should include multi-center data and add characteristic indicators to enhance the reliability of the results of this study.

CONCLUSION

The social support function of the primary caregiver of patients with AMI after interventional therapy was low and negatively correlated with anxiety and depression of the primary caregiver. For primary caregivers with anxiety and depression, timely attention and providing a deep examination of underlying issues should be provided to reduce adverse emotional distress, so that the caregiver can maintain a happy mood and implement care.

ARTICLE HIGHLIGHTS

Research background

After interventional therapy, most patients need care at home, from their caregivers. The social support function of primary caregivers is an important factor affecting the quality of care and prognosis of patients. Primary caregivers often experience varying degrees of anxiety and depression.

Research motivation

It is necessary to understand the correlation indicators of primary caregivers' social support functions to better guide clinical interventions. Considering that primary caregivers tend to have different levels of anxiety and depression, we speculate that their social support function may be related to anxiety and depression.

Research objectives

To explore the relationship between anxiety, depression, and the social support function of primary caregivers of patients with acute myocardial infarction (AMI) undergoing interventional surgery.

Research methods

Investigate the primary caregivers of AMI patients undergoing interventional surgery using the Social Support Rating Scale (SSRS), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS). The correlation between the SSRS and SAS or SDS was evaluated using a Pearson's correlation analysis, multiple linear regression, receiver operator characteristic curve (ROC), and area under the curve (AUC).

Research results

The SSRS was negatively correlated with the SAS and SDS scores. SAS and SDS were independent factors for low SSRS and could predict the risk of low SSRS.

Research conclusions

The social support function of primary caregivers of AMI patients undergoing interventional surgery is associated with anxiety and depression.

Research perspectives

Based on the Pearson's correlation analysis, multiple linear regression, ROC, and AUC, we comprehensively analyzed the correlation between the SSRS, SAS, and SDS scores of primary caregivers of patients with AMI who underwent interventional surgery, confirming that the social support function of primary caregivers is closely related to anxiety and depression, which is instructive for clinical intervention.

FOOTNOTES

Author contributions: Bao J designed the research and wrote the paper; Zou LT supervised the report; Wang XY contributed to the analysis; and Chen CH provided clinical advice.

Institutional review board statement: The study procedures were approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University (approval No. WXSY-YXLL-AF/SC-02/01.0).

Informed consent statement: All participants provided written and informed consent.

Data sharing statement: Raw data for this study can be obtained from the corresponding author.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to this checklist.

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ORIGINAL ARTICLE

Observational Study

Depression and sarcopenia-related traits: A Mendelian randomization study

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Abstract

BACKGROUND

Observational studies have suggested that depression is associated with sarcopenia. However, the causal relationship between depression and sarcopenia remains unclear.

AIM

To investigate the causal relationship between depression and sarcopenia.

METHODS

We performed a Mendelian randomization (MR) analysis to identify the bidirectional relationship between depression and sarcopenia-related traits. Summary-level data and independent variants used as instrumental variables came from large genome-wide association studies of depression (414055 cases and 892299 controls), of appendicular lean mass (ALM, 450243 participants), and of hand grip strength (exposure: 360000 participants; outcome: 334925 participants).

RESULTS

We identified a negative association of depression with lower ALM [odds ratio (OR): 0.932, 95% confidence interval (95%CI): 0.889-0.979, $P = 0.005$]. In the reverse MR analysis, we also observed an inverse association of hand grip strength with depression (OR: 0.200, 95%CI: 0.108-0.370, $P < 0.001$). Similar results were obtained in sensitivity analyses.

CONCLUSION

Depression was causally related to decreased muscle mass, and declined muscle strength might lead to a higher risk of depression.

Key Words: Appendicular lean mass; Depression; Hand grip strength; Mendelian randomization; Older adults; Sarcopenia

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Core Tip: In this Mendelian randomization study, we established a bidirectional relationship between depression and reduced muscle mass, specifically lower appendicular lean mass and hand grip strength. Our findings highlight a potential bidirectional relationship between depression and sarcopenia with implications for both mental and physical health.

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INTRODUCTION

Sarcopenia is a complex geriatric disorder marked by a gradual and progressive reduction of skeletal muscle mass, decrease in skeletal muscle strength, and deterioration in physical performance[1]. In addition to elevating the risks of disability, sarcopenia also relates closely to a wide range of adverse consequences, such as falls, hospitalization due to fall-related injuries, and even mortality[2,3]. As the population ages, the prevalence of sarcopenia increases, making it an important public health issue and a global health burden. In addition, depression is common among the elderly, with an average 12-mo occurrence rate of approximately 6%. This is related to negative health consequences, including increased mortality and reduced quality of life[4,5]. Thus, depression and sarcopenia are important concerns for the elderly population, and it is crucial to establish a clear understanding of their relationship.

Numerous observational studies have suggested that depression and sarcopenia are common comorbidities, but there is no direct evidence of causality[6-8]. In a clinical trial investigating sarcopenia as a therapeutic target, the management of sarcopenia was found to be associated with a notable reduction in depressive symptoms[9]. Some studies have suggested that skeletal muscle may influence psychiatric illnesses through neurotrophic factors[10]. However, those studies were unable to provide convincing evidence to elucidate a null association for the effect of depression on sarcopenia.

Mendelian randomization (MR) represents a compelling genetic epidemiological approach that utilizes genetic variants associated with exposures, which can effectively avoid the potential methodological limitations of observational studies, including reverse causation bias. We conducted this bidirectional MR study to examine the causal relationship between depression and sarcopenia.

MATERIALS AND METHODS

Study design

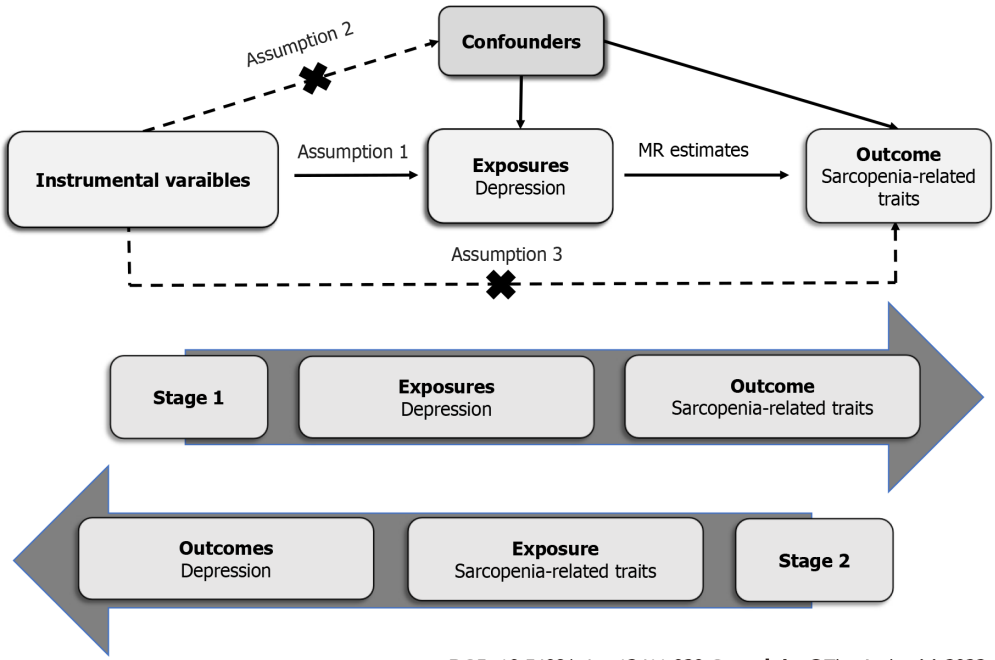
The diagram of this MR study is displayed in the Figure 1. The genetic variations selected as instrumental variables (IVs) were based on three predominant assumptions: (1) Selected IVs are strongly associated with exposures; (2) There is no observed association between the IVs and potential confounding factors; and (3) The IVs affect outcomes only through exposures without any other pathways[11].

IVs

The IVs for the MR analyses were derived from several different genome-wide association studies (GWASs). Single nucleotide polymorphisms (SNPs) were chosen as IVs when the SNPs for exposures reached genome-wide significance ($P < 5.0 \times 10^{-8}$). All IVs were clumped for independence (linkage disequilibrium $r^2 < 0.1$; region size, 3000 kb) according to the European data from the 1000 Genomes Project. If the SNPs for exposures were not available in the outcome datasets, proxy SNPs (linkage disequilibrium $r^2 > 0.8$) were adopted online (ldlink.nci.nih.gov/). Palindromic SNPs were excluded in the analyses when harmonizing the directions of SNP effects on exposures and outcomes. We also calculated the F-statistics to assess the instrument strength. IVs with F-statistics < 10 were considered to have a weak instrument bias.

Data sources

Genetic IVs associated with depression were obtained from a GWAS meta-analysis that included 414055 cases and 892299 controls from the UK Biobank, 23andMe_307k, and PGC_139k[12]. In the UK Biobank cohort, the depression phenotype, referred to as "broad depression," was determined based on self-reported responses to a web-based questionnaire. In the cohort from 23andMe_307k, the depression phenotype was determined based on self-reported information regarding clinical diagnosis or treatment for depression. In PGC_139k, the depression phenotype was clinically diagnosed. In total, this GWAS identified 102 independent SNPs located at 101 Loci that were associated with depression at a level of



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Figure 1 Principles of the Mendelian randomization study for depression and sarcopenia-related traits. MR: Mendelian randomization.

genome-wide significance, which led to an 8.9% variance in depression.

Appendicular lean mass (ALM) and hand grip strength were selected as a measure of muscle mass and strength. Unlike whole body lean mass, ALM is primarily affected by skeletal muscle and is recommended by the European Working Group on Sarcopenia in Older People due to its high predictive power for sarcopenia-related health outcomes [1]. The summary statistic for ALM was obtained from a GWAS of the UK Biobank (n = 450243)[13]. That GWAS had measured ALM by bioelectrical impedance analysis (BIA) for fat-free mass at the arms and legs. The summary statistic for hand grip strength was obtained from the UK Biobank (nealelab.is/uk-biobank) and included approximately 360000 participants from Europe. Right-hand grip strength (n = 359729) and left-hand grip strength (n = 359704) were meticulously assessed using a calibrated Jamar J00105 hydraulic hand dynamometer adjusted to accommodate hand size variations. We derived 139 independent genetic IVs associated with hand grip from a GWAS from the UK Biobank, which included 334925 individuals[14]. These variants accounted for 1.7% of the variability in grip strength. In this study, relative grip strength was applied, as it may show a better correlation with physical capability than absolute hand grip strength.

Each study incorporated in the GWAS used in the present study was approved by local research ethics committees or Institutional Review Boards, and all participants had given their informed consent.

Statistical analysis

In the main analyses, the random-effects inverse-variance weighted (IVW) approach was applied to evaluate a bidirectional relationship between depression and sarcopenia-related traits[15]. In addition, several sensitivity analyses were also conducted to identify potential pleiotropy. Cochran's Q test was used to assess the heterogeneity among various IVs. The weighted median method was used to include only valid IVs, allowing less than 50% of the genetic variants to be invalid IVs[16]. The MR-Egger method was conducted to detect and correct for any pleiotropic bias[17]. Furthermore, we used the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method to conduct a global test of heterogeneity and to identify horizontal pleiotropy. Any identified SNPs with pleiotropic effects were excluded, and a repeated IVW analysis was subsequently performed to ensure the robustness of the results[18].

All tests were two-sided, and the Bonferroni-corrected significance threshold was set to $P \leq 0.01$ (correcting for 5 outcomes) to account for multiple comparisons. The P values ranging from 0.05 to 0.01 were considered to be suggestive of a potential association between exposures and outcomes. All analyses were conducted using TwoSampleMR and MR-PRESSO packages in R software (Version 4.1.3).

RESULTS

The main characteristics of all SNPs adopted in the MR analyses are shown in Table 1. The F-statistics for all IVs were higher than the threshold of 10, indicating the absence of weak instrument bias in the present study. The summary information of SNPs for the three traits is displayed in Supplementary Tables 1 and 2. The results of Cochran's Q tests and MR-Egger regression are shown in Table 2.

Table 1 Studies and datasets adopted in the Mendelian randomization analyses

Trait	Data source	Sample size, cases/controls	Ancestry
Depression	UK Biobank[1]	127552/233763	European
	23andMe_307K[2]	75607/231747	
	PGC_139K[3]	43204/95680	
	Replication	474574/1032579	
Appendicular lean mass	UK Biobank[1]	450243	European
Hand grip strength, exposures	UK Biobank[1]	Approximately 360000	European
Hand grip strength, outcomes	UK Biobank[1]	334925	European

[1]UK biobank: (1) The broad definition of depression was used in the UK Biobank. Measured in a variety of ways, as follows: Have you ever seen a general practitioner for nerves, anxiety, tension or depression? and have you ever seen a psychiatrist for nerves, anxiety, tension or depression? and (2) Does not include the participants who were identified with bipolar disorder, schizophrenia, or personality disorder using self-declared data as well as prescriptions for antipsychotic medications.
[2]23andMe_307k: (1) The data were derived from the genome-wide association study results from the 23andMe Interactive Discovery projects; and (2) Depression was defined based on responses to web-based surveys, with individuals that self- reported as having received a clinical diagnosis or treatment for depression classified as cases.
[3]PGC_139k: (1) The PGC_139k cohort was obtained from the meta-analysis of major depressive disorder utilizing European-ancestry PGC cohorts with the 23andMe_307k and the previous UK Biobank cohorts removed; and (2) Depression was defined based on structured diagnostic interviews, or electronic medical records, with individuals that self-reported as having received a clinical diagnosis or treatment for depression.

Table 2 Results of potential pleiotropy and heterogeneity assessments in the bidirectional analyses

Parameter	Cochran's Q	*P* for Cochran's Q	Intercept	*P* for intercept
Outcome				
Appendicular lean mass	911.568	< 0.001	-0.002	0.602
Left hand grip strength	409.92	0.004	0.002	0.486
Right hand grip strength	379.511	< 0.001	0.002	0.243
Exposure				
Appendicular lean mass	1401.776	< 0.001	0.001	0.953
Hand grip strength	306.463	< 0.001	0.003	0.887

In the random-effect IVW estimates, genetically determined depression was causally associated with lower ALM [odds ratio (OR): 0.932, 95% confidence interval (95%CI): 0.889–0.979, $P = 0.005$; Figure 2]. This association was robust in the weighted median. The MR-PRESSO analysis identified 18 potential SNP outliers. After removing the outliers, the result was similar. There was significant association of depression with left hand grip and right hand grip (OR: 0.962, 95%CI: 0.936–0.989, $P = 0.007$; OR: 0.961, 95%CI: 0.935–0.987, $P = 0.004$). However, these results were not confirmed in the sensitivity analyses. Several potential SNP outliers were identified in the MR-PRESSO tests. After removing the outliers, the results remained significant.

A significant association was observed between decreased ALM and depression (OR: 0.969, 95%CI: 0.947–0.992, $P = 0.047$; Figure 3). In the sensitivity analyses, weighted median and MR-Egger tests revealed similar effects but with broader confidence intervals. Nine SNPs were detected in the MR-PRESSO test. After removing outliers, the result indicated a suggestive association (OR: 0.978, 95%CI: 0.957–0.999, $P = 0.044$). In addition, genetically determined hand grip strength was causally associated with depression by the IVW method (OR: 0.200, 95%CI: 0.108–0.370, $P < 0.001$). The weighted median method yielded similar results despite the MR-Egger test revealing a null association. In the MR-PRESSO test, three outliers were identified and removed, and the result remained significant.

DISCUSSION

We performed this MR study to explore the bidirectional causal association between depression and sarcopenia. In the forward MR analyses, depression was associated with decreased ALM. Results from IVW suggested that decreased ALM was associated with depression and that depression was associated with lower hand grip strength. However, these results could not be repeated in sensitivity analyses. In the reverse MR analyses, lower hand grip strength was associated with a higher risk of depression. Overall, we reported a significant bidirectional association between depression and

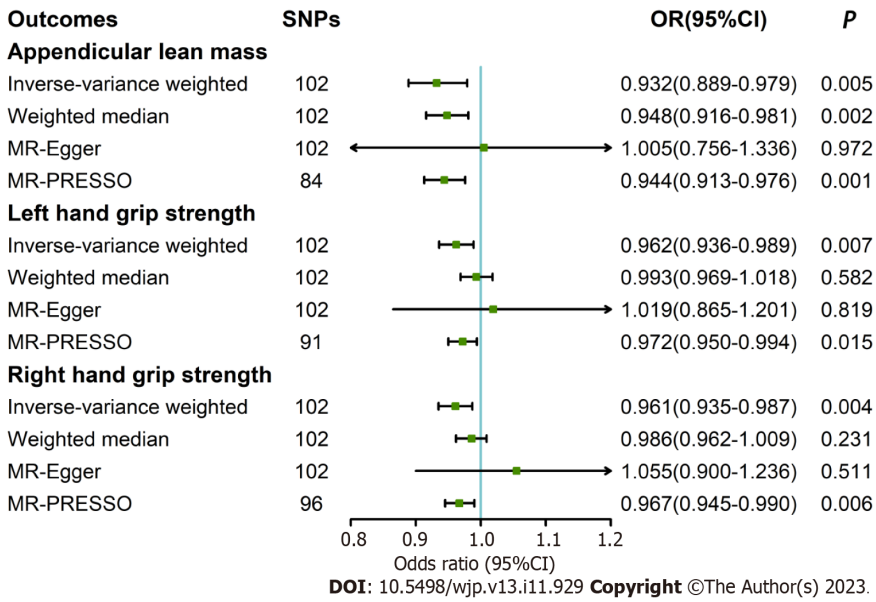


Figure 2 Effect of depression on sarcopenia-related traits. 95%CI: 95%confidence interval; OR: Odds ratio; PRESSO: Pleiotropy Residual Sum and Outlier; SNPs: Single nucleotide polymorphisms.

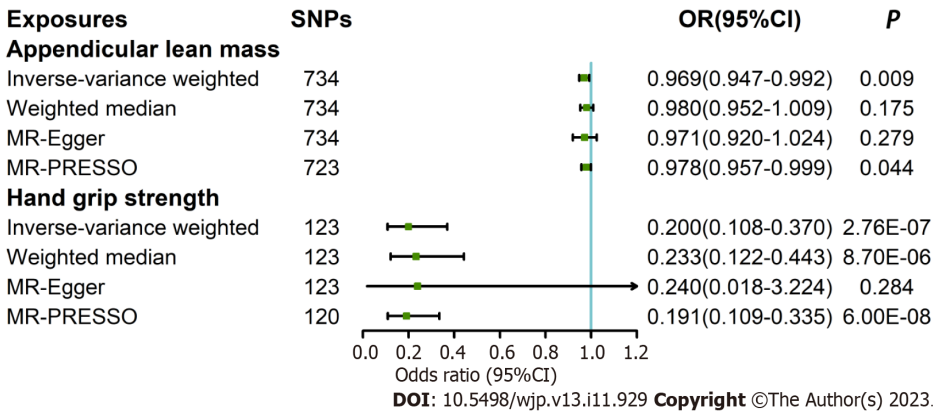


Figure 3 Effect of sarcopenia-related traits on depression. 95%CI: 95%confidence interval; OR: Odds ratio; PRESSO: Pleiotropy Residual Sum and Outlier; SNPs: Single nucleotide polymorphisms.

sarcopenia.

Previous observational studies, mainly cross-sectional in design, suggested that there was a positive association between depression and sarcopenia[8,19-22]. Two meta-analyses included also drew the conclusion that the prevalence of depression in patients with sarcopenia is higher than in the general population[6,7]. Despite considering many common covariates, these studies were still unable to provide evidence of causality between the two conditions. A recent longitudinal study comprising 115601 older adults reported that higher hand grip strength was associated with a lower risk of depression among older adults[23]. Similar results were also drawn from a 7-year prospective cohort study conducted in China[24]. Although this topic has received widespread attention, few studies have investigated the effect of depression on sarcopenia. Overall, our MR study provided evidence that depression and sarcopenia are possibly connected in a bidirectional manner, whereas previous studies primarily focused on investigating the effect of depression on sarcopenia in a unidirectional manner.

The exact mechanism between depression and sarcopenia remains inconclusive. However, there are several potential connections between the two conditions. First, in the original GWAS of hand grip strength, expression quantitative trait loci analyses revealed multiple genes associated with neurodevelopmental disorders or brain function[14]. The results of a meta-analysis demonstrated a significant enrichment of gene expression of brain-related transcripts[14]. In another study, researchers used twin data from China to explore the genetic overlap between depression and grip strength[25]. They observed potential genetic correlations, SNPs, genes, and pathways common to both conditions, which indicates a shared genetic basis[25]. Second, some studies have suggested that brain-derived neurotrophic factor secreted by skeletal muscle may play a role in depression and anxiety[10]. Brain-derived neurotrophic factor drives hippocampal neurogenesis, and the hippocampus is a key region of the brain implicated in psychiatric illness[26]. Third, chronic inflammation could potentially serve as a shared risk factor for both depression and sarcopenia[27]. Inflammatory biomarkers,

such as C-reactive protein and interleukin 6, are negatively associated with ALM[28]. Meanwhile, increased C-reactive protein and interleukin 6 are also associated with future depression[29]. This could be attributed to increased inflammatory cytokines in patients with sarcopenia, which could negatively impact the central nervous systems of older adults leading to a depressed mood and reduced mobility[27]. Finally, patients with depression are typically lacking in physical activity, which is a well-known factor leading to sarcopenia[30]. These findings collectively supported the conclusion of our current MR analysis, indicating a bidirectional relationship between depression and sarcopenia.

One of the key strengths of this analysis was the utilization of well-powered GWAS data for depression and sarcopenia-related traits. The implementation of a bidirectional MR design allowed for a comprehensive evaluation of the mutually causal relationship. Nevertheless, there are several limitations that need to be addressed. First, sample overlap between the exposure and outcome populations might potentially influence the study results. There was also a study, however, supporting the applicability of a single large dataset from large biobanks in two-sample MR studies[31]. Second, ALM was not directly measured by the BIA equipment but was estimated based on whole-body electrical conductivity. The estimates of BIA can be influenced by factors such as age, ethnicity, hydration status, and other related discrepancies. All of these factors may subsequently influence the MR results. Third, in the original GWAS the authors reported that they used the broad definition of depression in the cohort of the UK Biobank. This reporting mechanism differed from the self-declared clinical depression phenotype of the 23andMe_307k cohort and the clinically obtained phenotype of the PGC_139k cohort. This difference may have an impact on the results of the MR analysis. Fourth, the population in our study was restricted to Europe, which limits the generalizability of our findings to non-European populations. Finally, potential directional pleiotropy may contribute to bias in the estimation of causal inference even though MR-Egger regression and MR-PRESSO methods were applied.

CONCLUSION

We provided evidence of a bidirectional association between depression and sarcopenia. Depression was causally related to decreased muscle mass. Meanwhile, declined muscle strength might lead to a higher risk of depression. Our study highlighted the importance of assessing sarcopenia and depression among older adults to understand and address the interplay between physical and mental health.

ARTICLE HIGHLIGHTS

Research background

Sarcopenia is a complex geriatric disorder marked by a gradual and progressive reduction of skeletal muscle mass, decrease in skeletal muscle strength, and deterioration in physical performance. Depression is also common among the elderly. Observational studies have suggested that depression is associated with sarcopenia.

Research motivation

The causal relationship between depression and sarcopenia remains unclear.

Research objectives

To investigate the causal relationship between depression and sarcopenia.

Research methods

We performed a Mendelian randomization (MR) analysis to identify the bidirectional relationship between depression and sarcopenia-related traits. Summary-level data and independent variants were used as instrumental variables that came from large genome-wide association studies of depression (414055 cases and892299 controls), of appendicular lean mass (ALM, 450243 participants), and of hand grip strength (exposures: 360000 participants; outcomes: 334925 participants).

Research results

We identified a negative association of depression with lower ALM. In the reverse MR analysis, we also observed an inverse association of hand grip strength with depression. Similar results were obtained in the sensitivity analyses.

Research conclusions

Depression was causally related to decreased muscle mass. Declined muscle strength might lead to a higher risk of depression.

Research perspectives

Our findings highlighted a potential bidirectional relationship between depression and sarcopenia with implications for both mental and physical health.

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FOOTNOTES

Author contributions: Wang DK and Li YH drafted the initial manuscript, analyzed the data, and interpreted the results; Guo XM designed the study, analyzed the data, and critically revised the manuscript; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Safety and effectiveness of lurasidone in the treatment of Chinese schizophrenia patients: An interim analysis of post-marketing surveillance

Yu-Mei Wei, Xi-Jin Wang, Xiao-Dong Yang, Chuan-Sheng Wang, Li-Li Wang, Xiao-Ying Xu, Gui-Jun Zhao, Bin Li, Dao-Min Zhu, Qi Wu, Yi-Feng Shen

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Abstract

BACKGROUND

Schizophrenia is a psychiatric disorder characterized by chronic or recurrent symptoms. Lurasidone was licensed in China in 2019 for the treatment of adult schizophrenia in adults with a maximum dose of 80 mg/d. However, post-market surveillance (PMS) with an adequate sample size is required for further validation of the drug's safety profile and effectiveness.

AIM

To conduct PMS in real-world clinical settings and evaluate the safety and effectiveness of lurasidone in the Chinese population.

METHODS

A prospective, multicenter, open-label, 12-wk surveillance was conducted in mainland China. All patients with schizophrenia from 10 sites who had begun medication with lurasidone between September 2019 and August 2022 were eligible for enrollment. Safety assessments included adverse events (AEs), adverse drug reactions (ADRs), extrapyramidal symptoms (EPS), akathisia, use of EPS drugs, weight gain, and laboratory values as metabolic parameters and the QTc interval. The effectiveness was assessed using the brief psychiatric rating scale (BPRS) from baseline to the end of treatment.

RESULTS

A total of 965 patients were enrolled in the full analysis set and 894 in the safety set in this interim analysis. The average daily dose was 61.7 ± 19.08 mg (mean ± SD) during the treatment. AEs and ADRs were experienced by 101 patients (11.3%) and 78 patients (8.7%), respectively, which were mostly mild. EPS occurred in 25 individuals with a 2.8% incidence, including akathisia in 20 individuals (2.2%). Moreover, 59 patients received drugs for treating EPS during the treatment, with an incidence of 6.6% which dropped to 5.4% at the end of the treatment. The average weight change was 0.20 ± 2.36 kg (P = 0.01687) with 0.8% of patients showing a weight gain of ≥ 7% at week 12 compared with that at the baseline. The mean values of metabolic parameters and the QTc interval at baseline and week 12 were within normal ranges. The mean changes in total BPRS scores were -8.9 ± 9.76 (n = 959), -13.5 ± 12.29 (n = 959), and -16.8 ± 13.97 (n = 959) after 2/4, 6/8, and 12 wk, respectively (P < 0.001 for each visit compared with the baseline) using the last-observation-carried-forward method.

CONCLUSION

The interim analysis of the PMS of adult patients with schizophrenia demonstrate the safety and effectiveness of lurasidone in the Chinese population. No new safety or efficacy concerns were identified.

Key Words: Lurasidone; Safety; Effectiveness; Surveillance; Schizophrenia; Chinese

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Core Tip: We conducted the first post-marketing surveillance of the actual use of lurasidone in the treatment of patients with schizophrenia in real-world clinical practice since the drug was licensed in mainland China in 2019, and evaluated the safety profile and effectiveness of lurasidone in Chinese population. Here, we report an interim analysis based on 965 patients who received the medication between 2019 and 2022. This study hold significance as it contributes additional safety and effectiveness data on lurasidone beyond what was gathered in pre-marketing trials. Furthermore, it provides valuable reference information for clinical decision-making of schizophrenia treatment.

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INTRODUCTION

Schizophrenia is a psychiatric disorder marked by chronic or recurrent symptoms, often resulting in an impairment of social and occupational functioning. The characteristics of schizophrenia typically include incoherent or illogical

thoughts, delusions, hallucinations, unusual behaviors, and cognitive impairment[1]. Its global prevalence is approximately 1%, with an incidence of about 1.5 per 10000[2]. It is a highly disabling and costly condition, ranking among the top 10 burdensome diseases[3].

The goal of schizophrenia treatment is to reduce acute symptoms and prevent recurrence while maximizing the patient's quality of life[4]. Lurasidone is a second-generation antipsychotic drug with a high affinity for dopamine D_2, serotonin 5-$HT_{2A,}$ and 5-HT_7 receptors and a low affinity for H_1 and 5-HT_{2C} receptors. It is considered to be associated with relatively less side effects[5-7].

Lurasidone was licensed in mainland China in 2019 for the treatment of schizophrenia in adults, with a maximum dose of 80 mg/d. A series of clinical studies have been conducted to verify its efficacy and safety[8,9] and numerous clinical experiences have been accumulated for Chinese patients with schizophrenia since the launch. However, a post-market surveillance (PMS) for the drug with an adequate sample size is also required by the Chinese government. This study thus aimed to conduct a surveillance of the actual use of lurasidone among Chinese patients with schizophrenia in real-world clinical practice and evaluate the safety profile and effectiveness of the drug in the Chinese population. Here, we report an interim analysis based on 965 patients who received lurasidone between 2019 and 2022.

MATERIALS AND METHODS

Study design and population

This study represents an interim analysis of a 12-wk, prospective, observational, multi-center, open-label PMS conducted in China. Patients with schizophrenia from 10 sites across China who had begun treatment with Latuda® between September 2019 and August 2022 were enrolled. The patients were required to provide informed consent before participating. An electronic data capture system was used for the collection of diagnostic and treatment information such as details on drug use, adverse events (AEs), and other related parameters including but not limited to laboratory examinations. All patients who met the inclusion requirement were included in the full analysis set (FAS), whereas the safety set (SS) consisted of patients who had received at least one treatment and had data on safety indicators recorded after the treatment. The study protocol was approved by the ethics committees of Shanghai Mental Health Center (the leading site) and other sites.

Dose and concomitant therapy

The administered dose of lurasidone was decided by the treating physicians, typically initiating at 40 mg/d with no requirement for titration. Depending on the treatment response and tolerability, the dose could be increased to a maximum daily dose of 80 mg/d, according to the approved prescribing information in China (a dose of 160 mg/d is approved overseas). Because this study was non-interventional, concomitant therapy deemed essential by the physician was permitted and reported on the electronic Case Report Form, including but not limited to antipsychotic drugs, mood stabilizers, antidepressants, anxiolytics, and antiepileptics.

Safety evaluation

Safety analyses were based on the SS and evaluated by the frequency and severity of AEs that occurred during the trial. AEs were coded according to the International Council for Harmonisation International Dictionary of Medical Terms (MEDDRA 24.0, Medical Dictionary for Regulatory Activities). Assessments were made at visit 1 (week 0), visit 2 (weeks 2-4), visit 3 (weeks 6-8), and visit 4 (week 12) and were reported by the treating physicians. The assessment included the incidence of total AEs, extrapyramidal symptoms (EPS), akathisia, use of EPS drugs, and mean changes in weight from baseline. Adverse drug reactions (ADRs) were defined as AEs for which the participating physicians could not rule out lurasidone as the cause.

Effectiveness evaluation

The assessment of effectiveness was based on FAS and assessed by the change in the overall brief psychiatric rating scale (BPRS) score relative to the baseline at weeks 2-4/ weeks 6-8, and week 12. The BPRS is a scale that was created to assess clinical changes in patients with schizophrenia, with 18 items designed to represent discrete symptom areas. Items are rated on a 7-point Likert scale, from 1 = "not present" to 7 = "extremely severe", with the total scores ranging from 18 to 126 (calculated by summation of the item scores). The BPRS evaluates five areas: Anxiety-depression, anergia, thought disturbance, activation, and hostility-suspiciousness. Scores for the 5-factor model were also calculated[10].

Statistical analysis

The data were in the form of descriptive statistics as the study was non-interventional and were analyzed using R software version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are presented as frequencies and proportions and shown as *n* (%). Continuous variables are presented as mean ± SD and compared using paired *t*-tests, with $P < 0.05$ indicating statistical significance. Effectiveness endpoint data were analyzed using the last-observation-carried forward (LOCF) approach for the missing values.

Biostatistics statement

The statistical methods of this study were reviewed by a member of the Biostatistical Service from the Shanghai Medical Insight Technology Co., Ltd.

RESULTS

Patient characteristics and baseline demographics

A total of 965 participants were enrolled in the FAS. The SS comprised 894 participants after excluding 71 patients owing to a lack of AE documentation (Figure 1).

The baseline demographics showed that 39.2% of the patients were male and 60.8% were female. The average age was 35.4 ± 14.27 years and 7.5% of the patients were aged < 18 years. The average height was 166.1 ± 7.97 cm and average body weight was 66.0 ± 13.86 kg. Overall, 55.3% of the patients had obtained antipsychotic medication within 1 mo prior to the baseline (Table 1).

Dosing and concomitant medication

In the FSA comprising 965 patients, the mean exposure level of lurasidone was 5547.5 ± 3477.04 mg with 88.4 ± 40.98 exposure days and an average daily dose of 61.7 ± 19.08 mg during treatment. A total of 57.3% of the 949 participants in the FAS received concomitant medication during the surveillance, comprising drug (n = 520, 54.8%) and non-drug (n = 156, 16.4%) therapies. The number and proportion of patients in each treatment category are detailed in Table 2.

Safety of lurasidone

Overall, 101 (11.3%) and 78 (8.7%) of the 894 patients in the SS cohort developed AEs and ADRs, respectively. Most of these were mild AEs (n = 87, 9.7%) and ADRs (n = 65, 7.3%). Fourteen (1.6%) and 12 (1.3%) patients developed AEs and ADRs, respectively, prompting discontinuation, whereas the presence of SAEs was only reported in one patient (Table 3). According to the System Organ Class (SOC) classification, the most common SOC AEs were investigations and nervous system disorders, and the most frequent AEs were akathisia (n = 22, 2.5%), blood prolactin increased (n = 21, 2.3%), and nausea (n = 9, 1.0%) (Supplementary Table 1).

EPS: EPS ADRs occurred in 25 patients (2.8%); of these, 2.2% experienced akathisia, 0.8% acute dystonia, and 0.2% parkinsonism, as demonstrated by the subgroup analysis. No reports of tardive dyskinesia or other EPS ADRs occurred during treatment (Table 4).

Use of EPS drugs: In the SS, 59 of 894 participants used EPS drugs to reduce the incidence and severity of extrapyramidal side effects during the treatment period. The incidence was 6.6%, which dropped to 5.4% at the end of the treatment. The most frequent EPS drug used was Benzhexol, which was used by 46 patients (5.1%).

Weight gain: The mean body weights of the patients at baseline and week 12 were 66.21 ± 14.01 kg and 66.21 ± 13.70 kg, respectively, resulting in a mean weight change of 0.20 ± 2.36 kg. This weight change demonstrated statistical significance in the intra-group comparison (P = 0.0168). Furthermore, 7 (0.8%) patients were found to have gained ≥ 7% of their weight at visit 4 (Table 5).

Laboratory values: The mean values of glutamic-pyruvic transaminase (GPT), glutamic oxaloacetic transaminase, serum creatinine, fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and QTc interval were within normal ranges at baseline and had not significantly changed when measured at the week 12 visit, except for GPT (P = 0.0189) (Table 6).

Effectiveness of lurasidone

The changes observed in the total BPRS score indicated a significant improvement in the severity of schizophrenia throughout the course of the treatment. The total BPRS score stood at 43.6 ± 15.28 (n = 959) at baseline. Over the course of treatment, it progressively decreased to 34.7 ± 12.22 (n = 959), 30.1 ± 10.68 (n = 959), and 26.8 ± 9.58 (n = 959), respectively, at 2/4, 6/8, and 12 wk, with overall mean changes of -8.9 ± 9.76, -13.5 ± 12.29, and -16.8 ± 13.97, respectively (P < 0.001 for each visit compared with the baseline) based on the LOCF method. The changes in the 5-factor model scores exhibited a similar trend as the total BPRS score, with highly significant reductions in the score observed on each visit (P < 0.001) (Table 7).

DISCUSSION

Lurasidone is a novel benzisothiazole antipsychotic drug that was authorized by the FDA in 2010 for the treatment of adult patients with schizophrenia[5] and has been licensed in many other countries, including China in 2019. Numerous pre-marketing trials have been conducted, which have demonstrated the efficacy and safety of lurasidone[8,11-13]. However, pre-marketing research has limitations. These include a small sample size, difficulties in detecting AEs with low incidence but high severity during the trial phase, and relatively strict participant inclusion and exclusion criteria, preventing the participation of certain patients with specific diseases in the trials. Thus, safety issues may not be fully identified and the use of concomitant medication tends to be controlled, which is inconsistent with real-world clinical practice. The use of PMS is thus important to further evaluate the safety and effectiveness of drugs. This study represents the initial PMS of lurasidone conducted in a Chinese population. The interim analysis confirmed that lurasidone was effective, generally safe, and well-tolerated as a treatment option for schizophrenia in adult Chinese patients.

Table 1 Baseline demographics and clinical characteristics (*n* = 965)

Background factor	Category	*n* (%)
Sex	Male	378 (39.2%)
	Female	587 (60.8%)
Age	mean ± SD	35.4 ± 14.27
	< 18 yr	72 (7.5%)
	18 yr	892 (92.5%)
Height (cm)	mean ± SD	166.1 ± 7.97
Weight (kg)	mean ± SD	66.0 ± 13.86
Months since onset of first episode	mean ± SD	92.6 ± 113.95
Months since onset of current episode	mean ± SD	5.8 ± 55.52
Baseline BPRS score	mean ± SD	43.6 ± 15.28
Comorbidity of mental disorder besides schizophrenia	Yes	958 (99.3%)
Comorbidity besides mental disorder	Yes	848 (88.1%)
Antipsychotic medication within 1 mo prior to baseline	Yes	532 (55.3%)

BPRS: Brief psychiatric rating scale.

Table 2 Concomitant therapy (*n* = 949[1])

Category	*n*	%
All	544	57.3
Pharmacological therapy	520	54.8
Oral antipsychotic drugs	434	45.7
Injectable antipsychotics	12	1.3
Sedative-hypnotics/EPS drugs	112	11.8
Mood stabilizers/antiepileptic drugs	39	4
Antidepressants/anxiolytics	61	6.4
Other categories	105	11.0
Non-pharmacological therapy	156	16.4
ECT	12	1.3
rTMS	14	1.5
Other categories	142	15

[1]*n* = 949, number of patients in the full analysis set with concomitant therapy data documentation.
EPS: Extrapyramidal symptoms; ECT: Electroconvulsive shock therapy; rTMS: Repetitive transcranial magnetic stimulation.

Common adverse reactions of lurasidone include akathisia, EPS, somnolence, and nausea[14,15]. The most frequent treatment-emergent AEs (TEAEs) among Asian participants during a 6-wk study were found to be headache, constipation, akathisia, and nausea, with the latter two being more common in the 80 mg/d group compared with that in the 40 mg/d group[16]. During 26 wk of open-label extension treatment with lurasidone, the most frequently observed TEAEs were EPS, insomnia, akathisia, nasopharyngitis, schizophrenia, anxiety, nausea, and headache[17]. In the current PMS, the most frequently reported AEs included akathisia, elevated blood prolactin levels, and nausea, with the majority of the cases characterized as mild in severity. The pattern of AEs/ADRs identified in this interim analysis closely resembled the AE/ADR profile with the use of lurasidone 40 mg/d in previous trials for the treatment of schizophrenia [13]. The most frequently employed measures in response to EPS ADRs involve reduction of the antipsychotic drug, transitioning to antipsychotic drugs with a lower propensity to induce EPS, or utilization of specific medications designed for EPS treatment. In this study, the proportion of EPS drugs used during the treatment was 6.6%, which was higher than the incidence of EPS ADR (2.8%). The primary reasons for this could be attributed to two factors: (1) EPS treatment

Table 3 Summary of adverse events and adverse drug reactions (*n* = 894)

Category	*n*	%
Any AE	101	11.3%
Any ADR	78	8.7%
AE leading to discontinuation	14	1.6%
ADR leading to discontinuation	12	1.3%
EPS AE	29	3.1%
EPS ADR	25	2.7%
EPS AE leading to discontinuation	3	0.3%
EPS ADR leading to discontinuation	3	0.3%
Serious AE	1	0.1%
Serious ADR	1	0.1%

AE: Adverse event; ADR: Adverse drug reactions; EPS: Extrapyramidal symptoms.

Table 4 Percentage of participants with extrapyramidal symptom adverse drug reactions (*n* = 894)

Category	*n*	%
All	25	2.8%
Acute dystonia	7	0.8%
Akathisia	20	2.2%
Parkinsonism	2	0.2%
Tardive dystonia	0	0.0%
Other EPS ADR	0	0.0%

EPS: Extrapyramidal symptoms; ADR: Adverse drug reactions.

Table 5 Summary of weight gain (*n* = 894)

	Total
Baseline (mean ± SD)	66.21 ± 14.01
12 weeks (mean ± SD)	66.21 ± 13.70
Change in body weight (mean ± SD)	0.20 ± 2.36[1]
Weight gain from baseline ≥ 7%, *n* (%)	7 (0.8%)

[1]$P < 0.05$.

induced by antipsychotic drugs other than lurasidone in participants who were administered concomitant antipsychotics (47%); and (2) the utilization of prophylactic medications aimed at preventing patients from developing EPS during the course of treatment. The latter strategy is mainly aimed at patients who are susceptible to EPS (patients in the early stages of treatment and young males), to reduce their discomfort and improve compliance.

Lurasidone exhibits a strong affinity for dopamine D_2, 5-HT_7, and serotonin 5-HT_{2A} receptors. This favorable D_2/5HT_{2A} balance not only ensures the drug's antipsychotic effectiveness but also helps mitigate the EPS resulting from D_2 blockade [18]. Thus, as with other atypical agents, lurasidone has antipsychotic effects with limited EPS risk[14,19,20]. The incidence of EPS-related events (excluding akathisia and restlessness) was found to be 14.7% for lurasidone and 5.1% for placebo in short-term clinical trials[15]. In two long-term trials, the proportions of participants reporting EPS AEs in the lurasidone group during 12 mo of treatment were 12.9% and 11.9%, respectively[21,22].

Akathisia is one of the most frequent ADRs observed in multiple trials conducted in different regions. In a pooled analysis of European data from three randomized controlled trials (RCTs), the incidence of akathisia was 11.3%, representing 8.1% in the 40–80 mg/d group and 15.8% in the 120–160 mg group[23]. In the Asian population, the proportion of

Table 6 Changes in laboratory values from baseline to week 12

Measure	*n*	Mean	SD
GPT (U/L)			
Baseline	376	25.14	21.548
Week 12	109	27.33	20.624
Mean change	93	5.38[1]	21.705
GOT (U/L)			
Baseline	363	22.19	12.715
Week 12	108	24.39	12.565
Mean change	92	0.96	16.625
Serum creatinine (μmol/L)			
Baseline	370	65.86	16.383
Week 12	106	69.26	14.695
Mean change	90	1.21	10.854
Fasting blood glucose (mmol/L)			
Baseline	368	5.478	1.536
Week 12	101	5.451	1.5486
Mean change	84	-0.162	1.4467
Total cholesterol (mmol/L)			
Baseline	363	4.501	1.0389
Week 12	101	4.551	1.0888
Mean change	83	-0.079	1.1075
Triglycerides (mmol/L)			
Baseline	362	1.589	1.3002
Week 12	101	1.655	0.8413
Mean change	82	-0.207	1.3234
HDL cholesterol (mmol/L)			
Baseline	359	1.287	0.365
Week 12	99	1.308	0.3959
Mean change	82	0.073	0.415
LDL cholesterol (mmol/L)			
Baseline	344	2.694	0.8467
Week 12	90	2.746	0.7907
Mean change	73	-0.086	0.7312
QTc interval (ms)			
Baseline	280	415.6	93.41
Week 12	71	402	29.32
Mean change	57	-0.2	35.76

[1]$P < 0.05$.

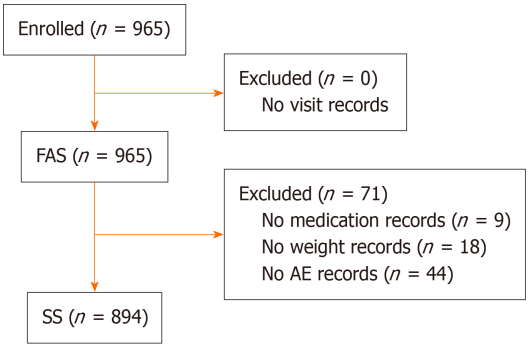
GPT: Glutamic pyruvic transaminase; GOT: Glutamic oxaloacetic transaminase; HbA1c: Glycosylated hemoglobin; LDL: Low-density lipoprotein; HDL: High density lipoprotein.

Table 7 Change from baseline to week 12 (last-observation-carried forward) in the total brief psychiatric rating scale score and 5-factor model score

BPRS (mean ± SD)	Baseline (*n* = 959)	2/4 wk (*n* = 959)	6/8 wk (*n* = 959)	12 wk ± 14 d (*n* = 959)
Total score	43.6 ± 15.28	34.7 ± 12.22	30.1 ± 10.68	26.8 ± 9.58
Change in total score	-	-8.9 ± 9.76[1]	-13.5 ± 12.29[1]	-16.8 ± 13.97[1]
Anxiety-depression	9.3 ± 4.00	7.6 ± 3.20	6.7 ± 2.75	6.0 ± 2.45
Change in anxiety-depression score	-	-1.6 ± 2.40[1]	-2.6 ± 2.94[1]	-3.3 ± 3.42[1]
Anergia	8.9 ± 3.55	7.5 ± 3.01	6.7 ± 2.75	6.2 ± 2.47
Change in anergia score	-	-1.4 ± 2.28[1]	-2.2 ± 2.69[1]	-2.8 ± 3.00[1]
Thought disturbance	10.7 ± 4.40	8.3 ± 3.49	7.1 ± 3.07	6.2 ± 2.79
Change in thought disturbance score	-	-2.4 ± 3.03[1]	-3.7 ± 3.77[1]	-4.5 ± 4.15[1]
Activation	5.9 ± 3.10	4.7 ± 2.35	4.2 ± 1.86	3.8 ± 1.58
Change in activation score	-	-1.2 ± 2.01[1]	-1.7 ± 2.41[1]	-2.1 ± 2.70[1]
Hostility-suspiciousness	8.8 ± 3.93	6.5 ± 2.85	5.4 ± 2.47	4.6 ± 2.17
Change in hostility-suspiciousness score	-	-2.3 ± 2.81[1]	-3.4 ± 3.42[1]	-4.1 ± 3.77[1]

[1]$P < 0.001$(paired *t*-test).

n = 959: Number of patients in the full analysis set with brief psychiatric rating scale data.



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Figure 1 Patient disposition. AE: Adverse event; FAS: Full analysis set; SS: Safety set.

patients that experienced akathisia was found to be 7.3% and 10.4% in the 40 and 80 mg/d groups, respectively, in another RCT that included mostly patients from East Asia[16]. In Chinese patients, the incidence of akathisia was reported to be 7.2% and 13.6% in patients treated separately with lurasidone and risperidone, respectively, by a pre-marketing RCT[8]. In the current PMS, the incidence of EPS ADRs was 2.8%; of these, 2.2% was contributed by akathisia, which is lower than the rates reported in previous studies. It is speculated that this inconsistency may result from three factors. First, the dosage of the drug. The development of akathisia was found to be dose-dependent in a previous trial [13]. In the current surveillance study, the average daily dose of lurasidone was 61.7 ± 19.08 mg, which is relatively low and, importantly, unlike pre-marketing clinical studies where fixed doses are commonly used, the treatment dosage in this PMS could be adjusted by the physicians based on the patient's tolerance, which may also help in reducing the occurrence of ADRs. Second, the concomitant medication. Drugs for treating EPS were allowed in the present study owing to its observational design of real-world clinical practice, and these medications may have led to reduced EPS and akathisia side effects. Last, sample size and monitoring requirements. Compared with pre-marketing RCTs, PMS studies typically entail larger sample sizes and involve less stringent monitoring protocols, which may occasionally result in a relatively lower proportion of AEs/ADRs reported by the participating physicians. However, a direct comparison of the data between these studies is generally not appropriate owing to differences in eligibility criteria and study methods.

Weight gain has been demonstrated to be a risk factor for treatment non-adherence in patients with schizophrenia[24,25] as it results in a worse quality of life, social exclusion, and increased stigma[26]. Moreover, a higher risk of developing metabolic syndrome (MetS) is linked to increased body weight[27,28]. A network meta-analysis of 100 RCTs comprising 25952 patients with schizophrenia found evidence of weight gain associated with the use of nine antipsychotics[29]. The reason why antipsychotic drugs induce weight gain remains unclear but might partly be ascribed to 5-HT_{2C}- and H_1-receptor affinity, which leads to hyperphagia and increased food intake[30,31]. However, lurasidone has only weak

affinity for 5-HT_{2C} receptors and poor or no affinity for histamine H_1[32]. Thus, the risk of weight gain might be relatively low from a mechanistic perspective, as confirmed by multiple clinical trials[33,34]. For short-term outcomes, 15 antipsychotic medications were evaluated for their effectiveness and tolerability by a meta-analysis of 212 trials and it was found that lurasidone, compared with placebo, is one of the only three drugs that did not lead to increased weight gain[33]. In terms of long-term outcomes, a pooled analysis of six studies showed that the mean weight change at month 12 was significantly greater in patients treated with risperidone and quetiapine extended-release (quetiapine XR) than those with lurasidone (+ 2.6 kg, + 1.2 kg *vs* − 0.4 kg)[34]. Previous trials did not find a dose-response relationship between the drugs and weight gain [11-13,16], and Wu *et al*[35] observed that the dose-response curve plateaued at 60 mg/d in a dose-response meta-analysis of 97 studies. In the current PMS, although the body weights of the patients at week 0 and week 12 were remarkably close (66.21 ± 14.010 kg *vs* 66.21 ± 13.696 kg), the number of participants with weight data recorded at these two visits varied (888 *vs* 801). Therefore, we used paired *t*-tests to analyze the mean change in weight, which was found to be 0.20 ± 2.356 kg at week 12 compared with the baseline paired population, showing a significant difference (P = 0.0168). However, this change remained minimal, and only 0.8% of patients showed a weight gain of ≥ 7% from baseline to week 12. Overall, in line with prior studies, there was a low chance of clinically significant weight gain in patients treated with lurasidone according to the results of the current PMS.

MetS is a collection of clinical and laboratory findings that are associated with an increased risk of cardiovascular disease[36]. The causes of MetS in patients with schizophrenia are not entirely elucidated, with antipsychotic drug side effects being a considered contributing factor[37]. Second-generation antipsychotics appear to be more likely to cause metabolic disturbances than first-generation antipsychotics, probably because of their affinity for the $5HT_{2C}$- and H_1-receptors as well as the M3 receptors that regulate the release of insulin, and thus maintain glucose homeostasis[37,38]. Previous studies have found that lurasidone is associated with a relatively low incidence of MetS[39,40]. The odds of developing MetS during the study period were significantly lower in patients receiving lurasidone than those treated with olanzapine and quetiapine XR in short-term treatment, and risperidone in long-term treatment, as demonstrated by a pooled analysis[41]. Despite the lack of a control group, the metabolic parameters of the study participants recorded at each visit in the current PMS were predominantly within the normal range, and a high proportion of those who were normal at baseline continued to remain normal during further follow-up visits (data not shown). This supports previous findings that lurasidone treatment has limited risk for adverse metabolic effects.

Hyperprolactinemia may be developed in patients with schizophrenia with or without antipsychotic medication[42]. Elevated prolactin levels induced by antipsychotic drugs are mainly associated with D_2 receptor affinity[43]. Several short-term studies have found no evidence of clinically significant changes in prolactin levels in patients treated with lurasidone[11-13]. A multicenter RCT conducted in mainland China showed that compared with the risperidone-treated group, the incidence of increased prolactin was remarkably lower in the lurasidone-treated group (3.1% *vs* 14.1%)[8]. In the current PMS, the incidence of increased prolactin was 2.3%, verifying that lurasidone has limited effects on prolactin levels, consistent with prior studies.

Lurasidone is a full antagonist of the dopamine D_2 receptor, with a receptor occupancy ratio of the latter after taking lurasidone 40 mg/d of 60%–80%, which is a prerequisite for its antipsychotic effectiveness[6]. Its targeting of the 5-HT_7 receptors can potentially enhance cognition by improving emotional regulation and sensory processing[6]. For acute phase treatment, a post hoc analysis of five studies in patients with acute schizophrenia found that lurasidone can reduce agitation early and sustainably, as measured by the PANSS-EC score[44]. Another meta-analysis of eight short-term RCTs confirmed that lurasidone was superior to placebo irrespective of positive or negative symptoms[45]. For maintenance treatment, an extension trial of 6 mo following a 6-wk acute-phase treatment of lurasidone showed further reduction and stabilization of the total PANSS score after receiving a flexible dose of lurasidone[46]. In terms of mood disorder, a pooled analysis of four studies verified significant improvement in depressive symptoms by lurasidone with greater decreases in MADRS score[47]. Overall, previous studies have supported the effectiveness of lurasidone in the treatment of schizophrenia and the interim analysis of the current PMS confirmed this conclusion, as supported by the continuous decrease in the total BPRS and the 5-factor model scores across all four visits during the surveillance period.

This study has some limitations. It was a single-armed, observational study with no control group, and the use of concomitant therapy, such as antipsychotic and EPS drugs, was allowed, which may represent confounders to the analysis and interpretation of the results. The sample sizes at each visit varied significantly and several participants did not provide their complete information, especially at visits 2 and 3. This may have an impact on the average of the measured data values and may not reflect the actual changes in the patients' condition. Although we used paired *t*-tests to partially address this issue, bias remains inevitable. The study period of this interim analysis was only 12 wk, and thus some AEs/ADRs that require a relatively long time to manifest may have not been observed and recorded during this period. It is worth mentioning that the study will be followed by a 12-month extension period, which we believe will provide further data support for clinical applications.

CONCLUSION

This preliminary data analysis from the PMS of lurasidone in adult patients with schizophrenia demonstrated its safety and effectiveness in a Chinese population, without emergence of any novel safety or efficacy issues. The study is ongoing and will facilitate continue to provide additional data and insights into the characteristics of lurasidone and its practical application in clinical settings.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a psychiatric disorder characterized by chronic or recurrent symptoms. Lurasidone was licensed in China in 2019 for the treatment of adult schizophrenia in adults.

Research motivation

To further validate the safety profile and effectiveness of lurasidone.

Research objectives

To evaluate the safety and effectiveness of lurasidone in the Chinese population.

Research methods

We conducted a prospective, multicenter, open-label, 12-wk surveillance in mainland China, and reported the interim analysis based on 965 patients who received the medication between 2019 and 2022.

Research results

Mean changes in total brief psychiatric rating scale scores were -8.9 ± 9.76 (n = 959), -13.5±12.29 (n = 959), and -16.8 ± 13.97 (n = 959) after 2/4, 6/8, and 12 wk, respectively (P < 0.001 for each visit compared with the baseline) using the last-observation-carried-forward method. adverse events and adverse drug reactions were experienced by 101 (11.3%) and 78 patients (8.7%), respectively, which were mostly mild.

Research conclusions

The interim analysis of the post-market surveillance demonstrate the safety and effectiveness of lurasidone in the Chinese population.

Research perspectives

This study contributes additional safety and effectiveness data on lurasidone, surpassing those obtained in pre-marketing trials. It offers essential guidance for clinical decision-making in the treatment of schizophrenia.

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FOOTNOTES

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Institutional review board statement: The study protocol was approved by the ethics committees of Shanghai Mental Health Center (the leading site) and other sites.

Informed consent statement: The patients were required to provide informed consent before participating.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Prospective Study

Treatment outcomes and cognitive function following electroconvulsive therapy in patients with severe depression

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Abstract

BACKGROUND

Traditional treatments for major depressive disorder (MDD), including medication and therapy, often fail and have undesirable side effects. Electroconvulsive therapy (ECT) uses electrical currents to induce brief seizures in the brain, resulting in rapid and potent antidepressant effects. However, owing to misconceptions and controversies, ECT is not as widely used as it could and often faces stigmatization.

AIM

To evaluate the efficacy and safety of ECT compared to those of medication and/or therapy in patients with severe MDD.

METHODS

This prospective cohort study included 220 individuals with severe MDD who were divided into the ECT and non-ECT groups. The patients in the ECT group underwent bilateral ECT three times a wk until they either achieved remission or reached a maximum of 12 sessions. The non-ECT group received medication and/or therapy according to clinical guidelines for MDD. The primary outcome was the variation in the hamilton depression rating scale (HDRS) score from treatment/ECT initiation to week 12. In addition, patients' quality of life, cognitive abilities, and biomarkers were measured throughout the study.

RESULTS

Although both groups showed significant improvements in their HDRS scores over time, the improvement was more pronounced in the ECT group than in the non-ECT group. Additionally, the ECT group exhibited a more substantial improvement in the quality of life and cognitive function than those of the non-ECT group. Compared with the non-ECT group, the ECT group exhibited evidently lower variations in the brain-derived neurotrophic factor (BDNF) and

cytokine interleukin-6 (IL-6) levels. The side effects were generally mild and comparable between the two groups. ECT is safer and more potent than medication and/or therapy in mitigating depressive symptoms, enhancing well-being, and bolstering cognitive capabilities in individuals with severe MDD. ECT may also affect the levels of BDNF and IL-6, which are indicators of neuroplasticity and inflammation, respectively.

CONCLUSION

ECT has emerged as a potentially advantageous therapeutic approach for patients with MDD who are unresponsive to alternative treatments.

Key Words: Alternative therapies; Biomarkers; Cognitive function; Electroconvulsive therapy; Major depressive disorder; Medication therapy

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Core Tip: Electroconvulsive therapy (ECT) is more efficient and safer in treating severe major depressive disorder (MDD) compared to medication and/or therapy. Here, ECT led to more pronounced improvements in depressive symptoms, quality of life, and cognitive function than non-ECT treatments. Additionally, ECT affected biomarkers related to neuroplasticity (brain-derived neurotrophic factor) and inflammation (interleukin-6). These findings highlight the potential of ECT as a therapeutic approach for individuals with severe MDD who do not respond to conventional treatments. By providing evidence of its beneficial outcomes, this study aimed to address the stigmatization surrounding ECT and facilitate its broader adoption in clinical practice.

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INTRODUCTION

Major depressive disorder (MDD) is a prevalent mental health condition with a profound impact on many individuals worldwide. The World Health Organization reported that MDD contributes significantly to the global health burden[1]. This condition is characterized by a persistent sense of sadness, diminished interest in daily activities, and a reduction in function that lasts for at least 2 wk. MDD can negatively affect physical, psychological, social, and occupational aspects of life, leading to increased morbidity, mortality, and suicide risk[2].

Conventional treatments for MDD include pharmacotherapy and psychotherapy, which aim to restore mood balance, reduce distress, and enhance coping strategies[3]. Pharmacotherapy involves the use of antidepressants, such as serotonin, dopamine, and norepinephrine, which act by targeting neurotransmitter systems[4]. Psychotherapy comprises a variety of psychological interventions that address the cognitive, behavioral, interpersonal, and emotional factors that contribute to depression[5]. Widely practiced and documented psychotherapy techniques include cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and supportive therapy[6]. However, conventional therapies are often insufficient and associated with adverse effects. Approximately 50% of patients achieve remission after a typical course of antidepressants, and approximately 30% remain resistant to multiple types of treatment[7]. Furthermore, antidepressants can cause adverse reactions, including nausea, weight gain, sexual issues, insomnia, and agitation[8]. Psychotherapy can also be ineffective or inaccessible to some patients because of a lack of availability, affordability, or motivation. Moreover, conventional therapies may take several wks or months before significant improvements are evident[9].

Electroconvulsive therapy (ECT) is a medical procedure performed under general anesthesia, using electrical currents to induce brief seizures in the brain. ECT has been used since 1938, primarily for treating schizophrenia, and was pioneered by Cerletti and Bini[10]. ECT has been widely used to treat many psychiatric disorders, particularly severe or treatment-resistant MDD[11]. It is a highly potent and safe remedy for acute or suicidal MDD, with remission rates ranging from 60% to 90%. ECT has been shown to improve the overall well-being and mental processing abilities of patients with severe MDD[11] and can produce rapid and robust antidepressant effects, with improvements observed within 1-2 wk[12].

However, ECT remains underutilized and stigmatized owing to misconceptions and controversies. Many patients and even some healthcare professionals have negative attitudes and beliefs concerning ECT, finding it cruel, dangerous, or outdated or believing that its effects can be substituted by long-term psychotherapy or hospitalization[13]. Some of these misconceptions are based on the historical use of ECT, which involves the delivery of large amounts of electrical charge, inadequate anesthesia, and frequent sessions, resulting in severe side effects, such as memory loss, brain damage, or death. However, modern ECT is a safe, effective, and regulated treatment that involves minimizing the amount of electrical charge delivered, administering adequate anesthesia, and designing patient-centered personalized sessions, resulting in minimal side effects, including transient headaches, nausea, and confusion[14]. Modern ECT does not cause

brain damage or permanent memory loss and would not affect the personality or intelligence of patients[15].

The primary objective of the present study was to compare the efficacy and safety of ECT with those of pharmacotherapy and/or psychotherapy in patients with severe MDD. We hypothesized that ECT would be superior to pharmacotherapy and/or psychotherapy in terms of improving the hamilton depression rating scale (HDRS) scores, a validated clinician-rated outcome measure for MDD. We also hypothesized that ECT would be superior to pharmacotherapy and/or psychotherapy in improving the quality of life and cognitive function in patients with severe MDD. Brain-derived neurotrophic factor (BDNF), cytokine interleukin-6 (IL-6), and cortisol levels were also measured as biomarkers of neuroplasticity and inflammation.

MATERIALS AND METHODS

Study design and participants

This prospective cohort analysis was conducted at The First Hospital of Hebei Medical University in China between January 2021 and June 2022. The research methodology was approved by the ethics boards of all involved institutions and strictly adhered to the Declaration of Helsinki and Standards for Reporting Observational Research. All participants provided written informed consent before participating in the study.

The study recruited individuals aged ≥ 18 years who had been diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders guidelines, had an HDRS score > 24 points, were willing to participate in the study, and attended subsequent visits. The exclusion criteria included a history of allergic reaction to ECT or anesthesia, prior neurological issues, brain trauma, seizure-related disorders, substance misuse or dependency in the past 6 mo, receiving any medication that may influence the seizure threshold or cognitive abilities in the preceding month (such as anticonvulsants, benzodiazepines, or antipsychotics), pregnancy or breastfeeding, diagnosis of any other mental or physical ailment that might affect the study results, or inability to provide blood samples for biomarker evaluation.

Eligible participants were allocated to the ECT and non-ECT groups depending on their treatment approach. In the ECT group, individuals underwent ECT as routine treatment for MDD. In the non-ECT group, individuals underwent drug therapy and/or psychotherapy (without ECT) as a routine MDD treatment. The treatment group was chosen at the discretion of the attending psychiatric team based on their clinical assessment and inclination. Participants were paired across groups based on age, sex, and HDRS scores at baseline.

Interventions

Participants in the ECT group underwent bilateral ECT using an apparatus specifically designed to deliver brief pulses (Thymatron System IV; Somatics LLC, Lake Bluff, IL, United States) according to a standardized protocol[16]. The protocol commenced with an initial assessment, including physical checkups, electrocardiography (ECG), blood testing, and cognitive evaluation. ECT was performed under general anesthesia using propofol and succinylcholine. Stimulus power was estimated using titration technique and fine-tuned according to the seizure duration and quality. ECT was administered thrice a wk until remission was achieved or a maximum of 12 sessions were completed. Vital signs, oxygen levels, ECG findings, and side effects were recorded during and after each ECT session.

The non-ECT group was treated with medication and/or psychotherapy according to the clinical guidelines for the treatment of MDD[17]. Medications included antidepressants (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors), mood balancers (lithium or valproate), and supplementary agents (thyroid hormones or antipsychotics). Psychotherapy included CBT, IPT, or supportive therapy. Medication type, dosage, length of course, and the use or absence of psychotherapy were determined by the attending psychiatrists based on patient feedback and tolerance.

Both groups were advised not to use other treatments or medications that could influence their mood or cognitive function during the study period. They were also encouraged to maintain their regular lifestyle and environment and report any physical changes or side effects to the research team.

Outcomes

The main metric of interest was the change in the HDRS score between the initial assessment and 12-wk mark. The HDRS consists of 17 clinician-evaluated items that measure the intensity of depressive signs[18]. Scores on the HDRS range from 0 to 52 points, with higher scores indicating more pronounced depression. A score of ≤ 7 points on the HDRS was considered to signify remission, a reduction of ≥ 50% from the initial score was considered a response, and a reduction of < 50% was classified as non-response.

Additional outcomes of interest included changes in quality of life, cognitive capabilities, and specific biomarkers between the baseline and 12-wk assessments. The World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire[19], a 26-item tool, was used to measure participants' quality of life and covered the domains of physical well-being, mental health, interpersonal relations, and the surrounding environment. The WHOQOL-BREF scores range from 0 to 100 points, with higher scores indicating higher quality of life. The Montreal Cognitive Assessment (MoCA) [20], a concise evaluation instrument, was used to gauge cognitive function, covering the areas of attention span, memory retention, linguistic skills, executive decision-making, and spatial cognition. The MoCA scores range from 0 to 30 points, with higher scores indicating greater cognitive ability. Blood samples collected at the ECT initiation and 12-wk mark were analyzed to measure BDNF, IL-6, and cortisol levels. BDNF is crucial for neuronal survival, differentiation, and adaptability. IL-6, a cytokine that promotes inflammation, is involved in immune reactions and mood and cognitive regulation. Cortisol, a hormone associated with stress, influences the hypothalamic (pituitary) axis and neuroendocrine

mechanisms. Any adverse reactions were documented during each visit and categorized as mild, moderate, or intense based on their severity and association with the study interventions.

Sample size

The required sample size was determined based on the primary outcome, HDRS, with an anticipated clinically meaningful difference of 5 points between the groups, a standard deviation of 10 points, a significance level of 0.05, and a statistical power of 0.8. Based on these criteria, we calculated that at least 100 individuals were required in each group to discern meaningful differences. Anticipating a 10% dropout rate, a prudent sample of 110 individuals was recruited from each group, totaling 220 participants.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, United States). Data normality was rigorously verified using histograms and Kolmogorov-Smirnov tests. Comparative analyses of the groups' baseline attributes were conducted using independent t-tests or Mann-Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical data. Changes in HDRS scores and secondary outcomes from baseline to 12 wk were assessed between the groups using analysis of covariance. Differences in means and 95% confidence intervals (CIs) were calculated using descriptive statistics. Adverse events between the groups were analyzed using chi-square or Fisher's exact tests. Statistical significance was set at $P < 0.05$.

RESULTS

Participant flow and characteristics

A total of 220 participants were recruited, of whom 110 were allocated to the ECT group and 110 to the non-ECT group. The participants' progress throughout the study is shown in Figure 1. Eight participants withdrew from each group due to personal choices or were lost to follow-up, culminating in 204 participants (102 in each cohort) included in the final analysis.

Table 1 presents the baseline attributes of the participants. No significant baseline differences were observed between the groups in terms of age, sex, MDD duration, MDD type, HDRS score, WHOQOL-BREF score, MoCA score, BDNF level, IL-6 level, or cortisol level (all $P > 0.05$).

Primary outcome

Table 2 displays the changes in HDRS scores from the initial assessment to the 12-wk mark. Both groups showed notable improvements in HDRS scores over time ($P < 0.001$ for both cohorts). The enhancement was significantly greater in the ECT than in the non-ECT group ($P < 0.001$). The average change in HDRS score between the cohorts was -5.4 (95%CI: -7.8 to -3.0), suggesting a substantial improvement in the ECT group.

Recovery by 12 wk was significantly higher in the ECT than in the non-ECT group (68% *vs* 42%, $P < 0.001$). Similarly, the rate of positive response by the 12th wk was also significantly higher in the ECT cohort than in the non-ECT cohort (86% *vs* 64%, $P < 0.001$). Conversely, the rate of no response by 12 wk was significantly lower in the ECT than in the non-ECT group (14% *vs* 36%, $P < 0.001$).

Secondary outcomes

Table 2 presents the variations in the quality of life, cognitive ability, and biomarker levels from the initial assessment to the 12-wk mark. Both participant groups exhibited notable enhancements in the WHOQOL-BREF and MoCA scores over time ($P < 0.001$ for both metrics and groups). However, the ECT group displayed significantly greater enhancement than the non-ECT group for both metrics ($P < 0.05$). The average difference between the groups was 6.2 points (95%CI: 3.4 to 9.0) for the WHOQOL-BREF and 1.6 points (95%CI: 0.8 to 2.4) for the MoCA.

Both groups showed a significant decrease in BDNF levels and a significant increase in IL-6 levels over time ($P < 0.001$ for both metrics and groups). However, these changes were significantly smaller in the ECT than in the non-ECT group for both metrics ($P < 0.05$). The average differences between the groups were -5.8 units (95%CI: -9.2 to -2.4) for BDNF and -1.2 units (95%CI: -2.1 to -0.3) for IL-6. None of the groups exhibited any notable changes in cortisol levels over the study duration ($P > 0.05$) or at the 12-wk mark ($P > 0.05$).

Adverse events

Table 3 shows that there were no significant differences in the occurrence of adverse effects between the two groups ($P = 0.62$). Commonly reported adverse effects included headache, nausea, dizziness, and memory issues, all of which were generally mild and short-lived. Moreover, throughout the study duration, no severe adverse effects were documented.

DISCUSSION

This study demonstrated that ECT is safer and more effective than pharmacotherapy and/or psychotherapy in alleviating depressive symptoms, improving well-being, and boosting cognitive ability in individuals with severe MDD. ECT also

Table 1 Baseline characteristics of the participants

Variable	ECT group (*n* = 102)	Non-ECT group (*n* = 102)	*P* value
Age (yr)	46.3 ± 11.2	45.8 ± 10.9	0.69
Sex (female/male)	58/44	60/42	0.81
Duration of MDD (mo)	24.6 ±12.8	25.4 ± 13.1	0.07
Type of MDD (unipolar/bipolar)	82/20	84/18	0.76
HDRS score	28.4 ± 3.6	28.2 ± 3.7	0.72
WHOQOL-BREF score	42.6 ± 8.9	43.1 ± 9.2	0.66
MoCA score	24.8 ± 3.2	25.1 ± 3.4	0.54
BDNF level (ng/mL)	18.6 ± 5.4	18.9 ± 5.7	0.62
IL-6 level (pg/mL)	3.4 ± 1.2	3.5 ± 1.3	0.58
Cortisol level (ng/mL)	12.7 ± 4.1	12.9 ± 4.3	0.71

Values are shown as average ± deviation or count. ECT: Electroconvulsive treatment; MDD: Major depressive condition; HDRS: Hamilton depression evaluation scale; WHOQOL-BREF: World Health Organization Quality of Life-BREF Assessment; MoCA: Montreal cognitive evaluation; BDNF: Brain-derived neurotrophic factor; IL-6: Interleukin-6.

Table 2 Changes in hamilton depression evaluation scale score and secondary outcomes from baseline to 12 wk, *n* (%)

Outcome	ECT group (*n* = 102)	Non-ECT group (*n* = 102)	*P* value
HDRS score	-19.6 ± 6.4 (-69)	-14.2 ± 7.2 (-50)	< 0.001
WHOQOL-BREF score	+15.4 ± 8.7 (+37)	+9.2 ± 7.9 (+21)	< 0.001
MoCA score	+2.6 ± 1.4 (+10)	+1.0 ± 1.2 (+4)	< 0.001
BDNF level (ng/mL)	-12.8 ± 4.6 (-69)	-18.6 ± 5.8 (-98)	< 0.001
IL-6 level (pg/mL)	+2.2 ± 0.9 (+65)	+3.4 ± 1.2 (+97)	< 0.001
Cortisol level (ng/mL)	-0.2 ± 3.8 (-2)	-0.1 ± 4.1 (-1)	0.92

Values are depicted as average ± deviation with percentage alteration in brackets. ECT: Electroconvulsive treatment; HDRS: Hamilton depression evaluation scale; WHOQOL-BREF: World Health Organization Quality of Life-BREF Assessment; MoCA: Montreal cognitive evaluation; BDNF: Brain-derived neurotrophic factor; IL-6: Interleukin-6.

appears to regulate the levels of BDNF and IL-6, which are biomarkers for neuroplasticity and inflammation, respectively.

These findings concur with those of previous studies highlighting the advantages of ECT over other treatments for patients with severe MDD. A meta-analysis of 16 randomized controlled trials (RCTs) involving 1391 patients with MDD found that ECT was more effective than pharmacotherapy or placebo in inducing remission and response[21]. Another meta-analysis of nine RCTs involving 619 patients with treatment-resistant depression found that ECT outperformed pharmacotherapy and placebo ECT in reducing the signs of depression[22]. Furthermore, a systematic review of 24 studies involving 1708 patients with MDD found that ECT produced greater improvements in patient well-being and cognitive abilities than other treatments[23].

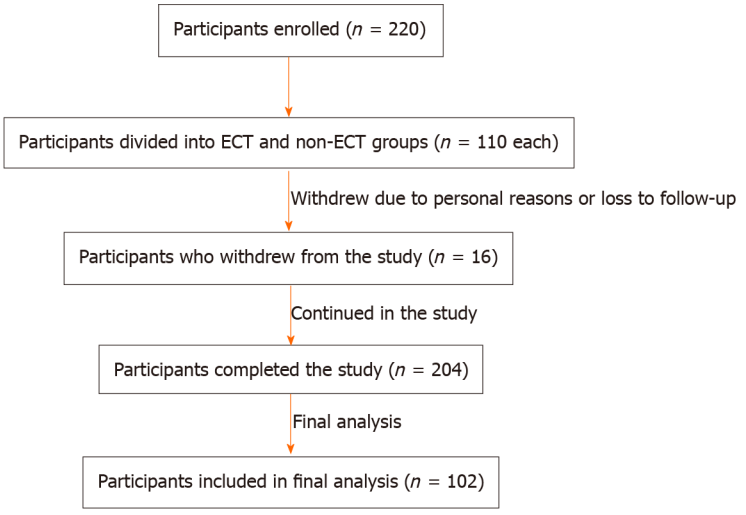
Although the precise mechanism underlying the action of ECT is unclear, it is likely related to its effects on the brain structure and function. ECT may induce neurogenesis, synaptogenesis, angiogenesis, and neurotrophic factor expression in multiple brain regions, particularly in the hippocampus, amygdala, and prefrontal cortex[24], which are involved in mood regulation, memory formation, and executive functions. ECT may also modulate neurotransmitter systems, including serotonin and dopamine, which are implicated in depression and cognition[25] and may normalize the hypothalamo-pituitary-adrenocortical axis activity and reduce the inflammatory response, both of which are associated with stress and depression[26,27].

The merits of the present study include its prospective cohort design, large sample size, use of a standardized protocol for ECT administration, use of validated and objective outcome measures, and long follow-up duration. The potential limitations of this study include its confinement to a single nation, absence of randomization and blinding of participants, potential variability in the prescribed pharmacotherapy and psychotherapy given to participants in the non-ECT group, and lack of assessment of other outcomes, such as cost-effectiveness or patient satisfaction.

Table 3 Adverse events reported by the participants, *n* (%)

Adverse event	ECT group (*n* = 102)	Non-ECT group (*n* = 102)	*P* value
Headache	32 (31)	28 (27)	0.54
Nausea	24 (24)	22 (22)	0.76
Dizziness	18 (18)	16 (16)	0.72
Memory impairment	14 (14)	12 (12)	0.69
Insomnia	10 (10)	14 (14)	0.39
Weight gain	8 (8)	10 (10)	0.63
Sexual dysfunction	6 (6)	8 (8)	0.57
Agitation	4 (4)	6 (6)	0.51
Confusion	2 (2)	2 (2)	> 0.99
Seizure prolongation[1]	2 (2)	N/A[2]	N/A[2]

Data are presented as number and percentage.
[1]Seizure prolongation was defined as a seizure duration > two min.
[2]Seizure prolongation was not applicable for the non-electroconvulsive therapy group. ECT: Electroconvulsive therapy; N/A: Not applicable.



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Figure 1 Participants' progress throughout the entire research process. ECT: Electroconvulsive therapy.

CONCLUSION

In conclusion, this study demonstrated that ECT is safer and more effective than pharmacotherapy and/or psychotherapy in enhancing signs of depression, overall well-being, and cognitive abilities in individuals with severe MDD, and in modulating the levels of BDNF and IL-6, which are biomarkers of neuroplasticity and inflammation, respectively. ECT may be a valuable treatment option for patients with MDD refractory to other treatments.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) is a prevalent mental health condition characterized by persistent feelings of sadness and loss of interest. Traditional treatments for MDD, such as medications and therapy, often have limited effectiveness and can lead to undesirable side effects. Electroconvulsive therapy (ECT) is an alternative treatment that uses electrical currents to induce controlled brain seizures, resulting in rapid and potent antidepressant effects. However, ECT is associated with misconceptions, controversies, and stigmatization, which hinder its wider acceptance and utilization.

Research motivation

The main theme of this study is to evaluate the efficacy and safety of ECT compared to medication and/or therapy in patients with severe MDD. The key problems that need to be addressed are the limited effectiveness and undesirable side effects of traditional treatments for MDD, which often lead to treatment failure. Despite its rapid and potent antidepressant effects, ECT faces misconceptions, controversies, and stigmatization, resulting in its underutilization.

Research objectives

The main objective of this study was to evaluate the efficacy and safety of ECT compared to medication and/or therapy in individuals with severe MDD. The specific goals accomplished were as follows: (1) Variation in the hamilton depression rating scale (HDRS) scores between the ECT and non-ECT groups over a 12-wk period; (2) improvements in the quality of life and cognitive function between the ECT and non-ECT groups were compared; (3) variations in the levels of brain-derived neurotrophic factor (BDNF) and interleukin-6 (IL-6), potential biomarkers of neuroplasticity and inflammation, respectively, between the ECT and non-ECT groups; and (4) evaluation of the safety and tolerability of ECT compared to medication and/or therapy. The achievement of these objectives has significant implications for future research. First, it provided evidence supporting the superior efficacy and safety of the ECT as a treatment option for individuals with severe MDD who do not respond to traditional therapy. This challenges the prevailing misconceptions and stigmatization surrounding ECT and encourages further investigation and acceptance of this modality. Second, the identification of biomarkers influenced by ECT opens avenues for future studies to explore the underlying mechanisms of its antidepressant effects and potentially identify predictors of treatment response. Overall, this study contributes to optimizing therapeutic approaches for severe MDD and guides future research toward better understanding and improved treatment outcomes for affected individuals.

Research methods

A prospective cohort design was used to achieve the research objectives. The study included 220 individuals with severe MDD who were divided into the ECT and non-ECT groups. In the ECT group, bilateral ECT was administered three times a wk until remission was achieved or a maximum of 12 sessions were reached. The non-ECT group received medication and/or therapy according to clinical guidelines for MDD. The HDRS score was used as the primary outcome measure, with variations in scores assessed from the beginning to 12 wk. In addition to the HDRS score, this study measured the patients' quality of life, cognitive abilities, and biomarkers throughout the study. The biomarkers of interest were BDNF and IL-6, which are indicators of neuroplasticity and inflammation, respectively. The collected data were analyzed using appropriate statistical methods, such as t-tests or analysis of variance, to compare the outcomes between the ECT and non-ECT groups. The study also assessed the safety and tolerability of ECT compared to medication and/or therapy by monitoring and documenting any side effects experienced by the participants. The novelty of this study lies in its comprehensive evaluation of the efficacy, safety, and biomarker influences of ECT compared to conventional treatments for severe MDD. By incorporating multiple outcome measures and biomarker assessments, this study provides a holistic understanding of the effects of ECT on depressive symptoms, well-being, cognitive function, neuroplasticity, and inflammation. This prospective cohort design allows the observation of treatment outcomes over time and contributes to a growing body of evidence supporting the potential advantages of ECT as a therapeutic approach for treatment-resistant MDD.

Research results

The results of this study indicated that ECT was more effective and safer than medication and/or therapy for severe MDDs. Both the ECT and non-ECT groups showed significant improvements in the HDRS scores over the 12-wk period. However, the ECT group demonstrated a more pronounced improvement in depressive symptoms than that of the non-ECT group. Moreover, the ECT group exhibited greater improvements in quality of life and cognitive function. The study also revealed that the ECT group had lower variations in the levels of BDNF and IL-6 compared with the non-ECT group. This suggests that ECT influences neuroplasticity and inflammation, potentially contributing to its therapeutic effects. These findings highlight the superior efficacy and safety of ECT as a treatment option for severe MDD, particularly in cases where traditional therapies fail. This study emphasizes the potential advantages of ECT in mitigating depressive symptoms, improving well-being, and enhancing cognitive capabilities. Furthermore, the exploration of biomarkers provides insights into the mechanisms underlying the effects of ECT and opens avenues for future research on personalized treatment approaches. Despite these positive outcomes, further investigations are required to address certain unresolved questions. Future studies should focus on the long-term effects, potential mechanisms of action, and comparisons between ECT and emerging treatment modalities. Further research is necessary to optimize therapeutic approaches, address stigmatization, and improve outcomes in patients with treatment-resistant MDD.

Research conclusions

The conclusions of this study indicate that ECT is a potentially advantageous therapeutic approach for individuals with severe MDD who do not respond to traditional treatments. This study found that ECT is safer and more potent than medication and/or therapy in mitigating depressive symptoms, enhancing well-being, and bolstering cognitive capabilities. This study also demonstrated that ECT may influence the levels of BDNF and the cytokine IL-6, indicators of neuroplasticity and inflammation, respectively. This study provides new evidence for the efficacy and safety of ECT as a treatment option for severe MDD and challenges the misconceptions and stigma surrounding this alternative therapy. These findings have implications for the development of new therapeutic approaches for MDD and underscore the need for further research in this area.

Research perspectives

Future studies in this field should focus on several aspects. First, further investigations are needed to examine the long-term effects of ECT on depressive symptoms, quality of life, and cognitive function in individuals with MDD. Longitudinal studies can provide valuable insights into the durability of the effects of ECT and its potential as maintenance therapy. Additionally, future research should explore the underlying mechanisms of ECT, particularly its influence on neuroplasticity and inflammatory markers such as BDNF and IL-6. Understanding these mechanisms could guide the development of targeted interventions and improve treatment outcomes. Moreover, studies should be conducted to directly compare ECT with other emerging treatments, such as transcranial magnetic stimulation or ketamine infusion therapy, to determine the most effective and personalized treatment options for different subgroups of patients with MDD. These research perspectives can contribute to advancing the field and optimizing therapeutic approaches for patients with severe MDD.

FOOTNOTES

Author contributions: Han KY, Wang CM, and Lv LZ were responsible for the study conception and design; Du CB and Qiao J provided administrative support; Han KY and Lv LZ provided the study materials and patients; Wang YL and Qiao J conducted data collection; Han KY and Lv LZ conducted data analysis and interpretation; All authors contributed to the manuscript writing process and granted final approval for the manuscript.

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ORIGINAL ARTICLE

Basic Study

Effectiveness of menstruation hygiene skills training for adolescents with autism

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Abstract

BACKGROUND

Adolescents with autism spectrum disorder (ASD) may encounter many difficulties with their menstrual cycles. Potential challenges that adolescents with ASD may face include understanding physical changes, coping with symptoms, emotional sensitivity, communication, personal care, and hygiene.

AIM

To evaluate the effect of menstrual hygiene skills training given to adolescents with ASD on their menstrual hygiene skills.

METHODS

The study was conducted with 15 adolescents diagnosed with ASD by the single group pre-test and post-test model in three special education centers in Türkiye. Data were collected with the Adolescent and Parent Information Form and the Adolescent-Specific Menstrual Hygiene Skill Registration Form.

RESULTS

While the mean age of adolescents was 16.06 ± 0.88 years, the mean age of individuals responsible for adolescent care was 43.66 ± 5.56 years. While 60.0% of the adolescents noticed the onset of bleeding before training, this rate was 93.3% after training. The Adolescent-Specific Menstrual Hygiene Skill Registration Form showed a statistically significant increase in the application steps after the training. The difference between the menstrual hygiene skill scores of adolescents

diagnosed with ASD before and after training was significant.

CONCLUSION

The menstrual hygiene skills training given to adolescents with ASD was beneficial in increasing their menstrual hygiene skills. These individuals must take responsibility during menstruation and independently manage their continuous care activities.

Key Words: Autism; Adolescent; Menstruation; Hygiene; Training

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Core Tip: Adolescents with autism spectrum disorder (ASD) may encounter many difficulties with their menstrual cycles. This study with 15 adolescents diagnosed with ASD by the single group pre-test and post-test model in three special education centers in Türkiye aimed to evaluate the effect of menstrual hygiene skills training given to adolescents with ASD on their menstrual hygiene skills. The menstrual hygiene skills training given to adolescents with ASD was beneficial in increasing their menstrual hygiene skills. These individuals must take responsibility during menstruation and independently manage their continuous care activities.

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INTRODUCTION

Adolescence is a transitional stage of development between childhood and adulthood. It is characterized by rapid physical, cognitive, emotional, and social changes. Most healthy adolescents adapt to this physical and psychosocial developmental process[1]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition definition, autism spectrum disorder (ASD) is a pervasive developmental disorder characterized by disorders in social interaction and communication and limited and repetitive behaviors, and causes limitations in the individual's daily life functions with its early symptoms[2]. The challenges faced by adolescents with ASD are multifaceted and can vary from person to person. Some difficulties faced by adolescents diagnosed with ASD are social difficulties, communication challenges, restricted and repetitive behaviors, sensory sensitivities, transitioning to adulthood, and mental health concerns. The transition to puberty can be particularly challenging for individuals with ASD. However, many of the challenges and experiences faced by individuals with ASD can be changed. Supportive interventions, individualized strategies, and a multidisciplinary approach can significantly help address these challenges and promote the well-being and development of adolescents with ASD[1,3,4].

Adolescents with ASD may encounter many difficulties with their menstrual cycles. Potential challenges that adolescents with ASD may face include understanding physical changes, coping with symptoms, emotional sensitivity, communication, personal care, and hygiene. They may have difficulty dealing with newly emerging situations such as foul odor, blood flow situation/feeling, and using sanitary pads, especially during menstruation[5]. If these changes are not adequately explained to adolescents with ASD, periodic crises and coping problems may occur. Even a simple skill like changing menstrual pads can become a complex motor skill for them[6]. It is essential to approach these challenges with sensitivity, individualized support, and an understanding of the specific needs and abilities of each adolescent with ASD. Collaborating with healthcare providers, educators, and caregivers can help create tailored strategies to address these challenges effectively[3,5,7,8].

A limited number of studies were found in the literature on menstruation periods in individuals with autism. One of these studies was conducted with two mentally disabled individuals[7]. There has been no study with a well-explained methodology and sufficient sample size that evaluates the effectiveness of training on menstrual hygiene skills with only a single focus group, such as adolescents with ASD. This study was planned to evaluate the effect of menstruation hygiene skill training given to adolescents with ASD on the ability to change and wear menstrual pads.

Research hypotheses

H_1: The menstrual hygiene skill level of the adolescent with ASD who is given menstrual hygiene skill training increases.

H_2: Menstrual hygiene skills training increases the independence of adolescents.

MATERIALS AND METHODS

Research design

This study was conducted in three special education centers in the provinces of Istanbul and Muğla between April 2022 and February 2023, using the "Single Group Pre-Test and Post-Test Model," which is one of the semi-experimental study methods. Creswell[9] sees the preference for single-group experimental design as necessary for the nature of the research in studies where a new training module is developed and applied.

Setting, participants, and recruitment

In calculating the sample size, studies compatible with the purpose and design of the research were examined. There is no research in the literature on the menstrual hygiene skill requirements of adolescents with ASD. Therefore, the research of Gölbaşi *et al*[10] on the effectiveness of peer education on menstrual hygiene with healthy adolescents was the basis for calculating the sample. According to this research, Menstrual Health Behaviors change was used in calculating the sample. When an increase of 5.69 points in the mean Menstrual Health Behaviors score was considered significant, the minimum sample size to be reached was 15. Since only the positive change in menstrual hygiene behavior was taken as the basis in our study, the sample size for this study was calculated as 15 adolescents with ASD using the G-Power software program with a margin of error of 0.05 and 80% power.

For this research, permission to conduct the study was requested from all special education units affiliated with the National Education in Istanbul and Muğla. However, only two private education institutions in Istanbul and one private education institution in Muğla granted permission for the research. The study was conducted in three centers affiliated with national education that had granted permission.

A total of 26 females with ASD were present across the participating institutions. Six females were excluded from the study: three females diagnosed with severe autism according to the Gilliam Autism Rating Scale-2 (GARS-2) score; and three females who were older than 18 years of age. Considering the data loss in the specified date range, 20 participants were invited to the research. Sample selection was not made. Three adolescents/parents did not volunteer to participate in the study, and two participants did not perform the post-test. As a result, 15 adolescents diagnosed with ASD were included in the study.

Inclusion criteria for the study were that the adolescent was diagnosed with ASD, the adult responsible for the adolescent's care was older than 18 years, and the adolescent was between the ages of 9-18 years (determined by considering the beginning of the menstrual cycle and the age of enrollment in special education centers), the adolescent's menstrual cycle started, the adolescent's hand washing skills, the adolescent's ability to fulfill instructions that require a single action, the adolescent's ability to watch visual stimuli such as projection shows, video viewing, *etc*, the adolescent's ability to perform the movements shown, the GARS-2 score as "mild" and "moderate," and the adolescent and the adult responsible for her care did not have hearing and visual impairment.

Data collection

Menstruation hygiene skills training: The training was a menstrual hygiene skill training in which visual methods and resuscitation methods were used to teach menstrual hygiene skills to adolescents with ASD. The training was given to the adolescents for half an hour 3 d a week. In each training group, two adolescents with ASD with similar characteristics and a teacher participated. Based on GARS-2 scores, adolescents with moderate autism were placed in one training group, while those with mild autism were placed in another training group. All training was completed in the same group, with the same teacher and researcher. The same researcher and a special education teacher gave the training in each training interview to standardize education. The training frequency, duration, and the number of participants were prepared with the recommendation of a pedagogue/psychologist so that adolescents could best understand and reinforce the skill. In addition, the researchers attended a seminar titled "Autism and Sexuality." For the visual method, a presentation consisting of only pictures prepared by the researchers was used. A pedagogue and special education teacher checked the suitability of the pictures in the presentation. A doll the size of an adolescent was used in the demonstration. With the help of this doll, the menstrual pad change skill was explained practically, and the adolescents were asked to repeat this skill (Table 1).

In addition to the training given to adolescents with ASD, video-assisted "Menstrual Hygiene Training: For Adults" was shown to the adults responsible for their care. Thus, individual differences in menstrual hygiene habits were minimized.

Procedure

Data were collected with the Adolescent and Parent Information Form and Adolescent-Specific Menstrual Hygiene Skill Registration Form, which the researchers created in line with the literature. First, training groups consisting of two participants with common characteristics were determined according to the adolescent's score and learning ability from the GARS-2. While determining the training groups, a consultation was received from the expert pedagogue and special education teacher. The pre-test and post-test of the study were performed by the individual responsible for the care of the adolescent. The aim of the research and how to use the data collection tools were explained to the individuals responsible for the care of the adolescents included in the study. A training video on menstrual hygiene was watched and then sent to the individual for viewing. In the first interview, the Adolescent and Parent Information Form and the Adolescent-Specific Menstrual Hygiene Skill Registration Form were administered to the participants included in the study through the individual responsible. In the post-test, only the Menstrual Hygiene Skills Registration Form was used. The individuals responsible for the care of the adolescents completed the post-test at home during the adolescent's first

Table 1 Application steps of changing sanitary pads

No	Steps
1	She noticed that she had started bleeding
2	She informed me about it
3	She either took off her clothes on her own or I helped her
4	She either removed her underwear on her own or I assisted her
5	She washed her hands
6	She retrieved a fresh pair of underwear
7	She opened the bag and took out a sanitary pad
8	She placed the sanitary pad onto her underwear without touching it directly, either by herself or with my assistance
9	She put on her underwear, either independently or with my help
10	She put on her pants, either by herself or with my assistance
11	She washed her hands and dried them using a towel
12	She realized that she needed to change her pad when the menstrual pad was dirty
13	She successfully removed the soiled pad
14	She either independently wrapped the dirty pad in her bag or I assisted her in doing so
15	She disposed of the dirty pad in the trash
16	She used toilet paper to wipe her perineum from front to back and discarded the used toilet paper in the trash
17	She took the clean, sanitary pad out of its bag and positioned it in her underwear
18	She put on her underwear and pants, either on her own or with my assistance
19	She washed her hands

menstrual cycle after training.

Data collection tools

Adolescent and parent information form: This form, which the researchers prepared, consisted of 11 questions to evaluate the sociodemographic characteristics of adolescents and parents, such as age, education status, income status, and menstrual pattern of adolescents (how many days they have menstrual bleeding and duration). The researchers filled this form with the face-to-face interview technique with the individuals responsible for the care of the adolescents.

GARS-2: The scale was used to determine inclusion criteria and training groups. The Turkish adaptation and validity and reliability studies of the scale were performed by Diken *et al*[11]. GARS-2 is a rating scale that aims to evaluate individuals aged 3–23 years who exhibit behaviors that characterize the autistic disorder. The GARS-2 is a Likert-type scale scored with an opinion-based four-point rating. GARS-2 consists of three subscales: stereotypical behaviors; communication; and social interaction. The scale consists of 42 items in total, with 14 items in each subscale. The highest score that can be obtained from the scale is 153, while the lowest score is 55. A high score indicates a high level of autistic disorder, while a low score indicates a low level of autistic disorder[11].

Adolescent-specific menstrual hygiene skill registration form: This form was created by researchers in parallel with Menstrual Hygiene Skills Training. This form was developed since no scale or form evaluates menstrual hygiene skills in the literature. Expert opinions from 10 individuals (academics in women's health and gynecologic nursing and pediatric nursing, psychologist, pedagogue, and special education teacher) were taken in developing and creating the form. The applicability and comprehensibility of the form were evaluated in a pilot study with five adolescent caregivers before the research data was collected. Incomprehensible items were renewed again. The adolescent was expected to complete 19 skill items in the form. Next to each skill item were "applied" and "not applied" options. In the form, "applied" was scored as 1 point and "did not apply" as 0 points. This scoring compared the pre-test and post-test. A minimum of 0 and a maximum of 19 points were taken.

Statistical analysis

Data were analyzed using the SPSS Statistics program (version 22; IBM Corp., Armonk, NY, United States). Descriptive statistics, mean, and standard deviation were used for continuous variables. Categorical variables were calculated as numbers and percentages. The normality of the distribution of the data was evaluated with the Shapiro-Wilks test, and it was found that the data were not normally distributed. Data were calculated as numbers and percentages before and after training and analyzed using the Wilcoxon signed-rank test. A statistical significance value of $P < 0.05$ was adopted.

Table 2 Descriptive characteristics of the adolescents

Descriptive characteristics	mean ± SD	Min-max
Age in yr	16.06 ± 0.88	15-17
Parent's age in yr	43.66 ± 5.56	36-52
Age of menarche	13.73 ± 1.09	11-15
Menstruation frequency in d	38.60 ± 39.25	21-180
Period of menstruation in d	5.13 ± 0.99	4-7
	n	%
Is the menstrual cycle regular?		
Yes	13	86.7
No	2	13.3
Adult caregiver		
Mother	14	93.3
Other	1	6.7
Adult education level		
Literate	1	6.7
Primary education	6	40.0
High school	8	53.3

SD: Standard deviation.

RESULTS

While the mean age of adolescents was 16.06 ± 0.88 years, the mean age of adults responsible for adolescent care was 43.66 ± 5.56 years. The mean age of menarche in adolescents was 13.73 ± 1.09 years, the frequency of menstruation was every 38.60 ± 39.25 d, the mean duration of menstruation was 5.13 ± 0.99 d, and the menstrual cycle of 86.7% of the adolescents was regular. The mothers of 93.3% of the adolescents were responsible for their care, and 53.3% of the adults were high school graduates (Table 2).

Table 3 shows the distribution of adolescents' menstrual hygiene skills before and after the training. While 60.0% of the adolescents noticed the onset of bleeding before the training, this rate was 93.3% after the training. Informing the adult about the application steps (80.0%), removing clothes/getting help (60.0%), removing underwear/getting help (66.7%), washing hands (73.3%), receiving clean underwear (66.7%), and removing the sanitary pad out of its bag (60.0%) reached 100% after the training. While the rate of placing the sanitary pad in underwear without touching anything or doing it with help was 60.0% before the training, it was 93.3% after the training. The steps of putting on underwear/getting help (60.0%), putting on pants/getting help (73.3%), and washing hands and drying with a towel (73.3%) reached 100% after the training. Before the training, 66.7% of the adolescents understood that the pad should be changed when it gets soil, while 73.3% understood it after the training. Being able to remove the soiled pad (60.0%), wrap the soiled pad in a bag or do it with help (66.7%), throw it in the trash (66.7%), wipe the perineum from front to back with toilet paper, throw the toilet paper in the trash (60.0%), removing the sanitary pad from its bag and placing it in the underwear (60.0%), putting on the underwear and trousers or doing it with help (86.7%), and washing hands (93.3%) reached 100%. The differences in the following steps of the menstrual hygiene training given to adolescents with ASD were statistically significant before and after the training: took off her clothes/did it with help (P = 0.014); took off her underwear/did it with help (P = 0.025); washed her hands (P = 0.046); took clean underwear (P = 0.025); took the menstrual pad and took it out of its bag (P = 0.014); put on the underwear/did it with help (P = 0.014); put on the pants/do it with help (P = 0.046); washed her hands and dried them with a towel (P = 0.046); took out the dirty pad (P = 0.014); wrapped the soiled pad in her bag/did it with help (P = 0.025); threw the pad in the trash (P = 0.025); wiped her perineum with toilet paper from front to back and threw the toilet paper in the trash (P = 0.014); and removed the sanitary pad out of its bag and placed it in her underwear (P = 0.014) (Table 3).

The difference between the menstrual hygiene skill scores of adolescents diagnosed with ASD before and after training was statistically significant (P < 0.005) (Table 4).

Table 3 Distribution of adolescents' menstrual hygiene skills before and after training

Application steps	Before training				After training			
	Applied		Not applied		Applied		Not applied	
	n	%	*n*	%	*n*	%	*n*	%
She noticed that she had started bleeding	9	60.0	6	40.0	14	93.3	1	6.7
She informed me about it	12	80.0	3	20.0	15	100	-	-
She either took off her clothes on her own or I helped her	9	60.0	6	40.0	15	100	-	-
She either removed her underwear on her own or I assisted her	10	66.7	5	33.3	15	100	-	-
She washed her hands	11	73.3	4	26.7	15	100	-	-
She retrieved a fresh pair of underwear	10	66.7	5	33.3	15	100	-	-
She opened the bag and took out a sanitary pad	9	60.0	6	40.0	15	100	-	-
She placed the sanitary pad onto her underwear without touching it directly, either by herself or with my assistance	9	60.0	6	40.0	14	93.3	1	6.7
She put on her underwear, either independently or with my help	9	60.0	6	40.0	15	100	-	-
She put on her pants, either by herself or with my assistance	11	73.3	4	26.7	15	100	-	-
She washed her hands and dried them using a towel	11	73.3	4	26.7	15	100	-	-
She realized that she needed to change her pad	10	66.7	5	33.3	11	73.3	4	26.7
When the menstrual pad was dirty								
She successfully removed the soiled pad	9	60.0	6	40.0	15	100	-	-
She either independently wrapped the dirty pad in her bag or I assisted her in doing so	10	66.7	5	33.3	15	100	-	-
She disposed of the dirty pad in the trash	10	66.7	5	33.3	15	100	-	-
She used toilet paper to wipe her perineum from front to back and discarded the used toilet paper in the trash	9	60.0	6	40.0	15	100	-	-
She took the clean sanitary pad out of its bag and positioned it in her underwear	9	60.0	6	40.0	15	100	-	-
She put on her underwear and pants, either on her own or with my assistance	13	86.7	2	13.3	15	100	-	-
She washed her hands	14	93.3	1	6.7	15	100	-	-

Table 4 Menstrual hygiene skills analysis and average scores of adolescents before and after training

Before training, mean ± SD (min-max)	After training, mean ± SD (min-max)	*P* (test value)
12.93 ± 5.52 (2-19)	18.60 ± 0.73 (17-19)	0.002 (-3.065)

SD: Standard deviation.

DISCUSSION

In this study, menstruation hygiene skill training was given to adolescents with ASD, video-based menstruation hygiene training was given to the individuals responsible for their care, and the hygiene skills of adolescents with ASD were revealed for the first time. The menstruation process in ASD-diagnosed adolescents was the same as in their healthy peers. These young people may have difficulty coping with emerging situations such as foul odor, blood flow situations/feelings, and using menstrual pads during menstruation. If ASD-diagnosed adolescents are not educated about these changes, periodic crises and coping problems can be seen in adolescents. When we look at the literature, the importance of training young people and their parents about the menstruation process is emphasized. However, young people with ASD remain in the background of this training process.

In many societies, the general viewpoint towards adolescents with ASD may cause the problems, especially during the menstrual period, to be ignored. Menstruation management of adolescents with ASD is complex and requires great patience. Menstruation hygiene skills are one of the biggest problems of adolescents with ASD and their caregivers. Communicating with adolescents with ASD is very important in terms of menstruation management. These young people face many complications during the menstruation process. In order to manage this process in the best way, adolescents and their caregivers should be taught to explain menstruation, physical changes, and especially hygiene

skills. One of the hygiene skills is noticing the start of menstrual bleeding. The current study applied menstrual hygiene skill training to adolescents with ASD. Most adolescents (93.3%) noticed the onset of menstrual bleeding after the training. In addition, all of the adolescents informed their caregivers that menstrual bleeding occurred after the training. In addition to the limited number of studies on this subject in the literature, the current study was consistent with the cross-sectional study of Rodgers *et al*[12] and the mixed-method study of adolescents with mental retardation[12,13].

Adolescents with ASD must be able to perform their daily routine and self-care skills to exist in society and continue their lives like healthy adolescents. For adolescents with ASD to continue their daily routines effectively in their communities, they must first have the ability to provide self-care and general hygiene and be able to dress independently. In particular, they should be able to change menstrual pads independently, which is an important aspect of self-care and menstruation management. Adolescents with ASD should be trained to develop skills and behaviors to acquire self-care skills. In the current study, it was observed that after the menstrual hygiene skill training, all of the adolescents took off their clothes and underwear by themselves or got help and were able to remove the menstrual pad from the bag before changing the menstrual pad. In addition, all the adolescents took out the soiled pad, wrapped it in their bags, and disposed of it properly after the training. In addition, after the training, it was determined that all adolescents with ASD completed the perineum cleaning properly by wiping their perineum with toilet paper from front to back. Another striking study result was that all participants washed their hands before and after changing the soiled pads after the training. In addition, while 60.0% of the adolescents could take the clean menstrual pad out of its bag and place it in their underwear before the training, it was observed that this rate was 100% after the training. According to the study results, adolescents' menstrual hygiene skill analysis scores before and after training increased significantly. In another practical study on dolls in Türkiye, pad-changing training was given to mentally retarded adolescents. It was observed that the training increased the pad-changing skills of adolescents[8]. In addition, the study results aligned with the limited study emphasizing the importance of menstruation training given to adolescents with special needs[14-17]. Further research must reveal the positive results of menstrual hygiene skills training given to adolescents with ASD.

CONCLUSION

In this study, menstruation hygiene skill training was given to adolescents diagnosed with ASD, and the effect of this training on the menstrual hygiene behavior of adolescents was evaluated. As a result of the study, it was observed that the self-care skills, such as hand washing and perineal cleaning especially in changing hygienic pads, of adolescents diagnosed with ASD increased after the training. With the successful results of this study, the importance of dividing the menstruation hygiene skill training into more than one step in adolescents with ASD and conducting this training in small groups became evident. Future research should focus on identifying developmentally sensitive pathways to reveal the voices of adolescents with ASD on their menstruation and puberty experiences. In addition, this study was one of the rare studies that increased the menstrual hygiene skills of adolescents with ASD by training groups of two participants with visual methods and demonstration methods.

Limitations

The present study had some limitations, and future researchers may consider addressing these as they explore this topic. First, this study focused only on ASD adolescents enrolled in special education centers. On the other hand, some adolescents diagnosed with ASD may be unable to access special education centers and face different difficulties. In addition, since the research data were collected from the people responsible for the care of adolescents with ASD, the information obtained may lead to positive or negative biases. The other limitation affecting the generalization of these results was the relatively small sample size. Nonetheless, the data obtained will serve as a valuable foundation for guiding future randomized controlled studies with a larger number of patients.

ARTICLE HIGHLIGHTS

Research background

Adolescents with autism spectrum disorder (ASD) may encounter many difficulties with their menstrual cycles. Potential challenges that adolescents with ASD may face include understanding physical changes, coping with symptoms, emotional sensitivity, communication, personal care, and hygiene. They may have difficulty dealing with newly emerging situations such as foul odor, blood flow situation/feeling, and using sanitary pads, especially during menstruation.

Research motivation

One of the important problems faced by adolescents with ASD during the menstrual period is to practice menstrual hygiene skills. This study was carried out in order to teach this skill to adolescents with ASD and to support their independence.

Research objectives

This study was planned to evaluate the effect of menstruation hygiene skill training given to adolescents with ASD on the

ability to change and wear menstrual pads.

Research methods

This study was conducted in three special education centers in the provinces of Istanbul and Muğla between April 2022 and February 2023, using the "Single Group Pre-Test and Post-Test Model," which is one of the semi-experimental study methods. Before the training, the Adolescent and Parent Information Form and the Adolescent-Specific Menstrual Hygiene Skill Registration Form were administered to the participants included in the study through the individual responsible. In the post-test, only the Menstrual Hygiene Skills Registration Form was used. The individuals responsible for the care of the adolescents completed the post-test at home during the adolescent's first menstrual cycle after training.

Research results

The mean age of adolescents was 16.06 ± 0.88 years. The mean age of menarche in adolescents was 13.73 ± 1.09 years, the frequency of menstruation was every 38.60 ± 39.25 d, the mean duration of menstruation was 5.13 ± 0.99 d, and the menstrual cycle of 86.7% of the adolescents was regular. The mothers of 93.3% of the adolescents were responsible for their care, and 53.3% of the adults were high school graduates. The difference between the menstrual hygiene skill scores of adolescents diagnosed with ASD before and after training was statistically significant ($P < 0.005$).

Research conclusions

It was observed that the self-care skills, such as hand washing and perineal cleaning especially in changing hygienic pads, of adolescents diagnosed with ASD increased after the training.

Research perspectives

With the successful results of this study, the importance of dividing the menstruation hygiene skill training into more than one step in adolescents with ASD and conducting this training in small groups became evident. In addition, this study was one of the rare studies that increased the menstrual hygiene skills of adolescents with ASD by training groups of two participants with visual methods and demonstration methods.

FOOTNOTES

Author contributions: Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to study design; Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to data collection; Yılmaz B contributed to data analysis; Kaydırak M contributed to study supervision; Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to manuscript writing; Kaydırak M, Yılmaz B, Azak M, and Bilge Ç contributed to critical revisions for important intellectual content; All authors read and approved the final manuscript.

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Institutional review board statement: Approval was obtained from the Muğla Sıtkı Koçman University Health Sciences Ethics Committee for the study (Protocol No. 200179/Decision No. 6). Permission was obtained from the special education centers where the research was conducted. The aim and method of the study were explained and informed to the individuals responsible for the adolescent's care, parents, and special education center staff. The purpose of the study, how the study would be carried out, that they could quickly leave the study whenever they wanted, and that the information received would be kept confidential was explained to the individuals responsible for the adolescent's care. The study was conducted in accordance with the Principles of the Declaration of Helsinki.

Informed consent statement: Written and verbal consent was obtained.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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CASE REPORT

Cerebrotendinous xanthomatosis presenting with schizophrenia-like disorder: A case report

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Abstract

BACKGROUND

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid-storage disorder caused by mutations in *CYP27A1*. Psychiatric manifestations in CTX are rare and nonspecific, and they often lead to considerable diagnostic and treatment delay.

CASE SUMMARY

A 33-year-old female patient admitted to the psychiatric ward for presentation of delusions, hallucinations, and behavioral disturbance is reported. The patient presented with cholestasis, cataract, Achilles tendon xanthoma, and cerebellar signs in adulthood and with intellectual disability and learning difficulties in childhood. After the characteristic CTX findings on imaging were obtained, a pathological examination of the Achilles tendon xanthoma was refined. Replacement therapy was then initiated after the diagnosis was clarified by genetic analysis. During hospitalization in the psychiatric ward, the nonspecific psychiatric manifestations of the patient posed difficulty in diagnosis. After the patient's history of CTX was identified, the patient was diagnosed with organic schizophrenia-like disorder, and psychotic symptoms were controlled by replacement therapy combined with antipsychotic medication.

CONCLUSION
Psychiatrists should be aware of CTX, its psychiatric manifestations, and clinical features and avoid misdiagnosis of CTX for timely intervention.

Key Words: Cerebrotendinous xanthomatosis; Psychotic symptom; *CYP27A1* gene mutation; Novel likely pathogenic variant; Case report

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Core Tip: Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid-storage disorder, characterized by diverse systemic and neuropsychiatric manifestations. Psychiatric manifestations in CTX are typically nonspecific, and past cases have reported a scarcity of psychotic symptoms, particularly delusions and hallucinations. In this report, we present a case of CTX exhibiting a hallucinatory-paranoid syndrome and describe the diagnostic and therapeutic processes associated with CTX. The long-term treatment effect in CTX may depend on age at start of treatment and psychiatrists should be cognizant of CTX to facilitate timely intervention.

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INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive inherited metabolic lipid-storage disorder related to bile acid biosynthesis pathways. It is caused by biallelic pathogenic variants in *CYP27A1* (2q35), which codes sterol 27-hydroxylase, a mitochondrial enzyme of the cytochrome P450 oxidase system. Reduction in the activity of this enzyme leads to an increased formation and storage of abnormal lipid content in several tissues, especially tendons, lenses, and the peripheral and central nervous systems. Typically, the affected individuals develop tendon xanthomas, cataracts, dementia, pyramidal paresis, cerebellar ataxia, and peripheral neuropathy. As epidemiologic data are limited and CTX may be substantially underdiagnosed, the prevalence of the disease is underestimated. No consensus exists on the prevalence of CTX, with an estimated rate of < 3:100000–5:100000 worldwide[1]. A recent worldwide genetic epidemiological study estimated the incidence of CTX to be 1:36042-1:468624 and highest among South Asians and East Asians, followed by North Americans, Europeans, and Africans[2]. The psychiatric manifestations of CTX are variable, with the most common manifestations being intellectual disability, behavioral disorders, and mood disorders. Few patients have delusions, hallucinations, paranoid ideas, or catatonia, similar to the features of schizophrenia. Thus, making a timely diagnosis is difficult for clinicians. Early diagnosis and treatment initiation in patients with CTX is of great importance because significant reversal of the disease progression could be achieved. Consequently, an enhanced understanding of this rare disease is necessary.

CASE PRESENTATION

Chief complaints

A 33-year-old woman was admitted to the psychiatric acute ward with the following symptoms: delusions of persecution, auditory hallucination, impulsive behavior, and emotional instability.

History of present illness

For 6 mo, the patient showed hostility towards her colleagues, firmly believing that they wanted to harm her. She could hear abusive voices of colleagues when she was alone. The false belief and voice interfered with the social relations and behavior of the patient, leading to outrunning behavior. In addition, the patient exhibited impulsive acts and temperamental behavior, such as tearing people's clothes, smashing things, standing outside naked when she became excited, and running around at midnight. She also experienced severe depression for several days, with crying and expressing a desire to commit suicide by euthanasia.

History of past illness

According to her mother, the patient has been weak and obtuse since childhood and was unable to pass primary school exams. She required supervision and care from her family in her personal life. Despite being able to work, she could not perform her job well and did not get along with her colleagues, leading to her dismissal from several companies. At age

18, she underwent cataract surgery, and at age 26, she underwent cholecystectomy for cholestasis.

A review of the patient's medical records revealed that she presented with swelling in her left Achilles tendon, pain, and skewed walking to the right side 5 years ago. Three years ago, she was admitted to the neurology department, where biochemical tests revealed an elevated total biliary acid level of 11.2 μmol/L (normal value ≤ 10.0) and decreased levels of chenodeoxycholic acid and ursodeoxycholic acid. Subsequently, a biopsy of the left Achilles tendon was performed, revealing numerous lipid crystals and a few foamy macrophages (Figure 1A). The patient underwent genetic analysis, which identified two mutations in the *CYP27A1* gene associated with CTX: c.1263 + 3G>C and c.379C>T. On the basis of these findings, the patient was ultimately diagnosed with CTX and prescribed chenodeoxycholic acid (750 mg/d) and rosuvastatin (10 mg/d).

Personal and family history

There was no family history of psychiatric diseases.

Physical examination

During hospitalization in the psychiatric ward, the patient's brief psychiatric rating sale (BPRS) score was 40, her Wechsler intelligence scale score was 65, and the total biliary acid returned to normal levels. Nervous system examination showed normal muscle tone in the extremities, grade 5 muscle strength, instability in the heel-knee-tibia test of the right lower extremity, and a positive Romberg sign. In the mental status examination, the patient exhibited the following: verbal auditory hallucination; delusions of persecution; negative perceptions; irritability; childish emotions; poor general knowledge, understanding, judgment, and calculation; impulsivity; and lack of insight.

Laboratory examinations

After nearly 3 years of adequate chenodeoxycholic acid treatment, the total biliary acid level returned to normal.

Imaging examinations

Brain magnetic resonance imaging (MRI) revealed symmetrical patchy abnormal signals in the dentate nuclei and deep medulla of the bilateral cerebellar hemispheres. These signals exhibited a slight decrease in signal intensity on T1-weighted images (T1WI) (Figure 2A) and a slight increase in signal intensity on fluid attenuated inversion recovery (FLAIR) (Figure 2B). Left-ankle-joint MRI showed that the inhomogeneous area had a considerable local thickening of the left Achilles tendon. The area displayed clear boundaries measuring approximately 6.6 cm × 1.2 cm and exhibited a slightly elevated signal intensity on T1WI and a similar slightly elevated signal intensity on the proton density weighted image, accompanied by linear hypointensity within (Figure 1B). Brain magnetic resonance spectroscopy (MRS) showed decreases in N-acetylaspartate (NAA) intensities and increases in lactate and lipid signals (Figure 2C and D).

FINAL DIAGNOSIS

In accordance with International Classification of Diseases-10 criteria, the patient received the following diagnoses: Organic schizophrenia-like disorder and CTX.

TREATMENT

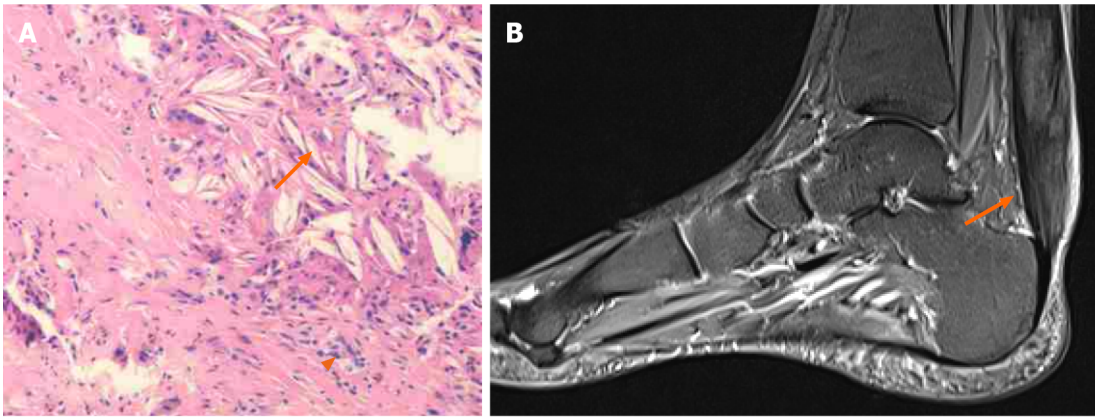
Concurrent with chenodeoxycholic acid treatment for the primary condition, we administered olanzapine to manage the patient's psychotic symptoms, and sodium valproate to stabilize mood while augmenting the antipsychotic medication.

OUTCOME AND FOLLOW-UP

After treatment, the psychotic symptoms were remarkably relieved, her emotions were relatively stable, and impulsive or noisy behavior did not manifest itself. The reassessed BPRS score was 21. During the 3-mo outpatient follow-up, the patient took medication on time and occasionally experienced emotional fluctuations but was able to listen to persuasion and did not exhibit any more impulsive behavior or running.

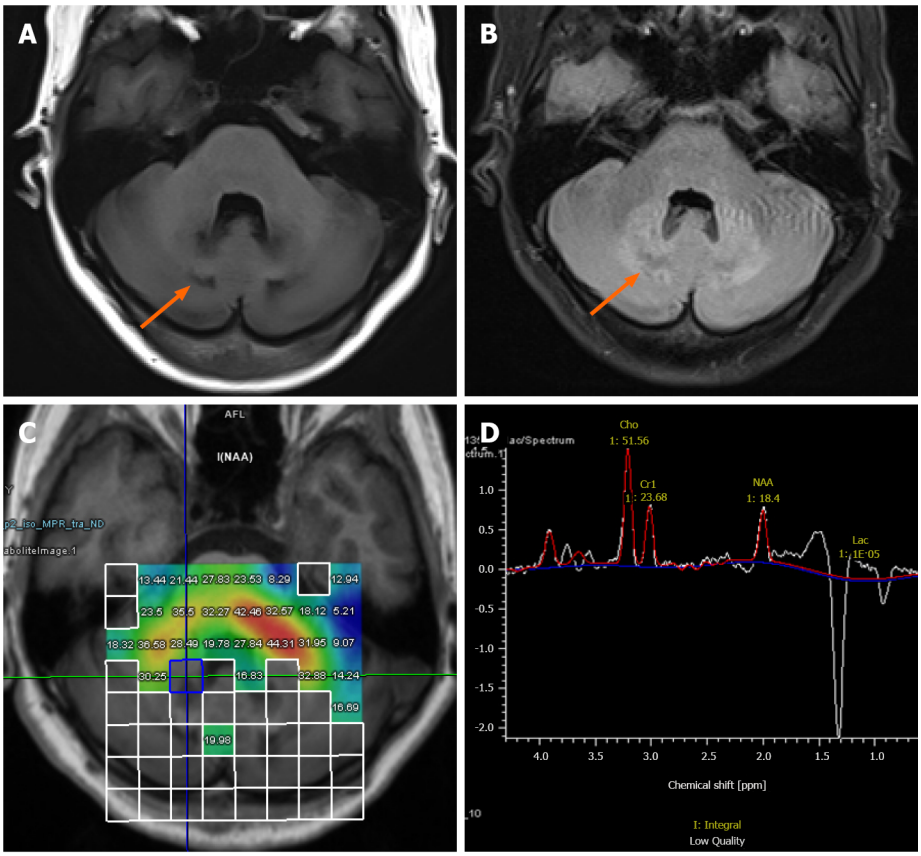
DISCUSSION

The clinical presentation of CTX is characterized by diverse systemic and neuropsychiatric manifestations and combinations of symptoms that vary from patient to patient. Of these, psychiatric disturbances are considered a strong diagnostic indicator of CTX, but the symptoms are so variable, as in this case, that making a timely diagnosis is difficult for clinicians. CTX is estimated to have a 15–20-year diagnostic delay[3,4].



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Figure 1 Imaging of left ankle joint and histopathological analysis of the resected specimen. A: Histological findings of left Achilles tendon xanthoma shows foamy macrophages (arrowheads) and lipid crystal (arrows); B: Left ankle joint magnetic resonance imaging reveals a mild increase in signal intensity on the proton density-weighted image, accompanied by linear hypointensity within.



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Figure 2 Brain imaging findings. A: Brain magnetic resonance imaging reveals patchy symmetrical abnormal signals in the dentate nuclei and deep medulla of bilateral cerebellar hemispheres and a slight decrease in signal intensity on T1 weighted image; B: Slight increase in signal intensity on fluid attenuated inversion recovery; C: Magnetic resonance spectroscopy shows right cerebellar dentate nuclei; D: Decreases in N-acetylaspartate intensities and increases in lactate signals and lipid signals.

The lack of specificity of the early clinical symptoms of CTX is the main reason why the disease is difficult to diagnose in a timely manner, and clinicians must often consider the clinical features of multiple systems, biochemical tests, and radiological examination. Among them, the dentate nucleic signal change in MRI is considered a strong diagnostic indicator[3]. The distinctive neuroradiological findings of CTX show symmetrical abnormalities in the bilateral cerebellar dentate nuclei region with a low signal intensity on T1WI and a high signal intensity on T2 weighted image and FLAIR. The brain MRS shows decreases in NAA intensities and increases in lactate signals[5]. The gold standard for diagnosing CTX is the analysis of the *CYP27A1* gene. In the present case, two mutations were confirmed in the *CYP27A1* gene by

genetic sequencing, with c.379C > G being previously reported as pathogenic and considered one of the most frequent mutations in the Chinese population[6]. However, the relationship between the unreported mutation at the c.1263 + 3G > C locus and the CTX disease phenotype must be further explored.

The psychiatric manifestations of CTX among the Chinese population are infrequently discussed, but foreign literature suggests that intellectual disability, attention deficit hyperactivity disorder, and autism spectrum disorder are often present in childhood or adolescence, with mood and impulsive behavioral symptoms becoming more prominent in adulthood[7]. In the present case, the patient exhibited psychiatric manifestations consistent with those in previous studies. A notable detail that the patient also exhibited hallucinatory-paranoid syndrome, which was scant in past cases and is the first description in Asian population[8]. Psychotic manifestations in CTX are rare, especially in younger patients, and they are often misattributed to psychiatric disease. Most of the psychiatric manifestations of CTX appear after xanthomas and neurological symptoms[7], allowing psychiatrists to identify this organic disorder more easily. Chenodeoxycholic acid is currently the first-line treatment for CTX, and its combination with antipsychotic medication may be beneficial for most patients if psychotic symptoms are present[8]. In the present case, the bile acid level returned to normal after nearly 3 years of adequate chenodeoxycholic acid treatment. The psychiatric symptoms remarkably improved after the combination of the antipsychotic olanzapine and the mood stabilizer sodium valproate during hospitalization. Moreover, the condition was stable at the 3-mo follow-up, indicating that such drugs have good efficacy on psychiatric symptoms associated with CTX.

The long-term treatment effect in CTX may depend on the age at start of treatment. At a point in time demarcation, two different therapeutic effects were observed. A study showed that patients with CTX who started chenodeoxycholic acid treatment before the age of 24 have a better prognosis[9], whereas a follow-up revealed minimal progression in MRI imaging compared with baseline[10].

CONCLUSION

In psychiatric clinical practice, patients with intellectual disability come to the clinic because of concomitant psychiatric behavioral symptoms, and psychiatric specialists need to pay attention to the differential diagnosis, especially when patients are found to have Achilles tendon xanthomas, juvenile cataracts, childhood-onset chronic diarrhea, and cholestasis. Thus, further improvement of biochemical tests, such as serum cholestanol, radiological examination of the Achilles tendons and brain, and genetic analysis, is needed to avoid a missed or misdiagnosis of CTX for timely intervention.

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FOOTNOTES

Author contributions: Ling CX and Xu XJ conceived the concept of this article; Gao SZ, Li RD, Gao SQ, Zhou Y provided the clinical insights in this case; Ling CX wrote the first draft; Xu XJ contributed to conducting the critical revision of the article and served as the corresponding author; All authors approved this manuscript.

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REVIEW

Risk factors, preventive interventions, overlapping symptoms, and clinical measures of delirium in elderly patients

Xi Mei, Yue-Hong Liu, Ya-Qing Han, Cheng-Ying Zheng

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Abstract

Delirium is an acute reversible neuropsychiatric syndrome caused by multiple factors. It is associated with many adverse clinical outcomes including cognitive impairment, functional decline, prolonged hospitalization, and increased nursing service. The prevalence of delirium was high in department of cardiology, geriatric, and intensive care unit of hospital. With the increase in the aged population, further increases in delirium seem likely. However, it remains poorly recognized in the clinical practice. This article comprehensively discusses the latest research perspectives on the epidemiological data, risk factors, preventive interventions, overlapping symptoms, and clinical measures of delirium, including specific measures to manage delirium in clinical real-world situations. This article helps readers improve their knowledge and understanding of delirium and helps clinicians quickly identify and implement timely therapeutic measures to address various delirium subtypes that occur in the clinical settings to ensure patients are treated as aggressively as possible.

Key Words: Delirium; Risk factors; Preventive interventions; Research progress; Review; Clinical practice

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Core Tip: This paper reviews the whole delirium process and its latest research progress in risk factors, preventive interventions, identification of superimposed symptoms, and clinical measures to provide a comprehensive and systematic account of delirium and present the latest medical information. This article helps readers improve understanding of delirium and helps clinicians quickly identify and take timely therapeutic measures to address the various delirium subtypes that occur in the clinic setting. This is to ensure that patients can be treated as aggressively as possible.

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INTRODUCTION

Delirium is a group of syndromes characterized by acute changes in attention, consciousness, and cognitive function that cannot usually be attributed to pre-existing neurocognitive disorders. According to ICD-11, delirium is an acute or subacute onset of attention deficit (*i.e.*, diminished ability to direct, focus and maintain attention) and impaired consciousness (*i.e.*, diminished orientation to the environment), with symptoms often fluctuating throughout the day with other cognitive deficits (*e.g.*, memory, language, visuospatial function, or perceptual deficits) that can interfere with the sleep-wake cycle; the etiology is often nonpsychiatric behavioral disorders, substance or drug intoxication or withdrawal.

Regarding delirium incidence, epidemiological data vary across countries or regions, medical scenarios, and assessment methods[1]. In Table 1, the highest delirium incidence was found in post-surgical patients, intensive care unit (ICU) patients, and patients with dementia, with extremely high incidence in the elderly population with dementia (up to 56%), postcardiac surgery patients (range: 11%-46%), and patients in the ICU ward (range: 19%-82%).

Delirium leads to increased treatment needs, longer hospital stays, and increased burden of care for patients, with extremely high medical costs. However, 30%–40% of delirium cases can be prevented[1-3]. Therefore, a comprehensive and systematic understanding of the entire delirium process is important for preventing and responding to its occurrence. This study reviews the whole delirium process and its latest research progress in risk factors, preventive interventions, identification of superimposed symptoms, and clinical measures to provide a comprehensive and systematic account of delirium and to present the latest medical information.

LITERATURE REVIEW METHODOLOGY

A search of PubMed and EMBASE databases was performed in July 2022. The search strategy focused on terms for "delirium AND risk factors AND epidemiology," "delirium AND preventive interventions," "delirium AND overlapping symptoms," "delirium AND clinical measures," and "delirium AND prevention and therapy" in 10 years. Although 8290 papers were initially evaluated, only those that fulfilled the following criteria were included in the study: (1) The article was published in English; (2) The trials included original data, as full articles in peer-reviewed journals were included; (3) The studies were representative of the general population or of specific patient populations; and (4) When two or more articles reported data from the same study sample, only the most relevant article was considered. Ultimately, 128 articles were retrieved, which were manually examined for relevance, and 89 articles were identified for further assessment.

RISK FACTORS

Delirium is usually not triggered by a single factor. Patients are often exposed to multiple risk factors, broadly classified into inherent (or predisposing) and controllable risk factors (or precipitating)[4]. Identifying various factors, such as brain tissue hypoxia, inflammation, and drowsiness triggered by sedation, and controlling them can help prevent or improve delirium[5]. Patients with more inherent risk factors can trigger delirium with the action of a few controllable factors[6,7].

Predisposing factors

Advanced age: Delirium is very common among hospitalized older adults; however, its etiology remains unclear[6]. With increase in age, organs deteriorate, and brain and cerebrovascular functions decline even in a non-diseased individual[8]. Neurons use glucose provided by the cerebral microvascular system to produce ATP *via* glycolysis as an energy uptake pathway[9]. The accumulation of neuronal and cerebral microvascular damage throughout life disrupts the energy uptake pathway, leading to inadequate energy uptake and decreased energy metabolism in the brain or specific areas of the brain. This can result in dysfunction in various ways and lead to delirium development in older individuals[10].

Cognitive decline or impairment: Dementia and neurodevelopmental delay are risk factors for delirium. Patients with Alzheimer's disease have a relatively high risk of delirium. Delirium occurred at a significantly higher rate in patients with faster cognitive decline than in those with slower cognitive decline[11]. The same higher prevalence of delirium exists for neurodevelopmental delays in childhood[12]. This evidence confirms that a low cognitive level is a risk factor for delirium.

History of delirium: The duration of delusions varies greatly among individuals, with most cases lasting a few days and some lasting several months. Persistent delirium is not uncommon, with 20% of patients still having some symptoms 6 mo after delirium onset[13]. In such cases, the likelihood of delirium recurrence is extremely high. Patients who have experienced delirium once are more likely to experience delirium again. Moreover, delirium maybe a predictor of

Table 1 Incidence and prevalence of delirium

Country or region/manuscript type	Medical scenario	Assessment method	Incidence (%)	Prevalence (%)
United States[1]	Community	NR	NR	1-2
Italy[79]	Community	DSM-5	NR	3.6
Spain[80]	Community	DSM-4	NR	0.96
Jordan[81]	Postcardiac surgery	CAM-ICU	9	NR
Poland[82]	Postcardiac surgery	DSM-5 (age ≥ 65 yr)	21.4	NR
		DSM-5 (age ≥ 80 yr)	33.5	NR
Czech[83]	ICU	CAM-ICU	26.1	NR
Systematic review[84]	ICU	Hyperactive	4	4
		Hypoactive	11	17
		Mixed	7	10
Canada[85]	Dementia Ward	CAM (MMSE ≥ 10)	1.6	3.4
		CAM (MMSE < 10)	6.9	33.3
Italy[86]	Dementia Clinic	CAM	NR	13.3
Australia[87]	Hospice care	DSM-5	40.2-45	42-88
Systematic review[88]	Hospice care	NA	29	35
Australia[89]	Post-stroke (3 d)	DSM-4	25	NR
Portugal[90]	Post-stroke (1 d)	DRS	2	NR
Systematic review[25]	Post-stroke	NA	NR	13-48
Holland[91]	Psychiatric Outpatient Clinic	DRS-R98 (probable)	NR	19
		DRS-R98	NR	2

NR: Not reported; NA: Not available; ICU: Intensive care unit; DSM: Diagnostic and Statistical Manual of Mental Disorders; DRS: Delirium Rating Scale; CAM: Confusion Assessment Method.

cognitive decline and dementia[14]. History of delirium is common in patients with Alzheimer's disease dementia and dementia with Lewy bodies[15].

History of emotional disturbance: Severe depressive symptoms in preoperative patients were significantly associated with higher delirium incidence[16]. A cohort study showed that depression and post-traumatic stress disorder severity were positively associated with delirium duration during a 3-mo follow-up[17].

History of alcohol abuse: During alcohol withdrawal, norepinephrinergic hyperexcitability causes symptoms such as increased blood pressure, tremors, and anxiety, which can be controlled with adrenergic agonist drugs[18]. Such drugs are also used to prevent delirium in elderly patients undergoing cardiac surgery or other procedures, including clonidine or dexmedetomidine treatment[19]. Opioids increase norepinephrine release, thereby increasing the risk of delirium development[20,21]. The use of benzodiazepines in the clinical management of alcohol withdrawal syndrome has been associated with disrupted sleep patterns and delirium[22].

Malnutrition: Nutritional deficiency is a risk factor for delirium development[23]. Preoperative malnutrition is correlated with postoperative delirium. Moreover, elevated nutrition levels may reduce the risk of postoperative delirium[24].

Visual and auditory impairment: Visual and hearing impairment increases risk of delirium; in general medical patients, the risk of delirium is 2.1-3.5 times higher in patients with visual impairment than in those without. In contrast, in surgical patients, the risk of delirium is 1.1 and 1.3 times higher in patients with visual and hearing impairment, respectively[1].

Other factors: Other factors include frailty, cardiovascular disease, cerebral atrophy, white matter disease, low education level, male sex, and comorbidities[10].

Precipitating factors

Brain function impairment: Delirium is affected by various factors of brain function, including cerebrovascular injury [25], altered metabolic levels in the brain[26], neurotransmitter imbalance[27], and damage to brain network connections

[28,29]. Excessive microglial activation, impaired endothelial barrier function, and blood-brain barrier dysfunction may be associated with delirium and severe cognitive impairment[30].

Acute somatic diseases: Acute somatic illnesses such as sepsis, hypoglycemia, and liver failure can increase the risk of delirium[31]. Septicaemia-related encephalopathy is a common neurological complication of sepsis that is poorly understood and is associated with increased morbidity and mortality. The clinical manifestations of the disease ranges from mild confusion and delusion to severe cognitive impairment and deep coma[30]. Recent popular theories such as the brain-gut axis, brain-kidney axis, and brain-spleen axis suggest that physical health can affect brain function to a certain extent[32,33].

Infection: Patients who develop delirium after infection show a significant increase in the presence of synaptic damage markers[34]. Patients with neocoronary pneumonia may also develop cerebral hypoxia and delirium[35].

Drug use: Drug use and withdrawal, including changes in medication use, are associated with delirium. Benzodiazepines, dihydropyridines, L-type calcium channel blockers commonly used to treat hypertension, antihistamines, and opioids may pose a high risk of delirium[36].

Sleep rhythm disorders: Sleep rhythm disturbance and sleep deprivation are important factors in delirium development in ICU patients[37]. Sleep disorders and delirium share many symptoms, and their similarity has led to the belief that they are highly correlated[38].

Electrolyte imbalance: Electrolyte imbalance is a risk factor for delirium. Studies have reported that in 53 patients with delirium with serum electrolyte imbalance, correction led to a significantly shorter delirium duration in 18 patients than in 35 patients without electrolyte correction[39].

Environment: The probability of delirium increases by being in a 24-h light environment in the ICU ward or by changes in the senses, including vision and hearing, due to environmental changes[40].

Pain and surgical anesthesia: Both pain and anesthetic drug use for pain relief may trigger delirium; however, the interaction between the two and the extent of their contribution to delirium remains unclear[36]. A multicenter randomized clinical trial, among patients over 65 years old with fragile hip fractures, reported no significant difference in the incidence of delirium between general anesthesia and regional anesthesia within 7 d after surgery[41].

Other factors: Other factors include poor feeding, drug combinations, lack of communication, and physical restraint (physical activity restriction).

PREVENTIVE INTERVENTIONS

Prevention, targeting controllable factors, can effectively control delirium, including reducing its incidence by avoiding functional brain damage or preoperative precautions. Yale University School of Medicine conducted a randomized controlled trial for delirium prevention that demonstrated the feasibility of a multimodal non-pharmacologic protocol to reduce the delirium incidence from 15% to 9%[4]. In this study, the delirium prevention protocol focused on managing the following six risk factors: disorientation, inactivity, sleep deprivation, visual impairment, hearing impairment, and dehydration. This prevention program also applies to healthcare settings such as nursing homes[42]. The long-term care plan adaptation for elderly patients with high delirium risk factors in the geriatric ward care can effectively prevent delirium[43].

Non-pharmacological approaches to effective delirium prevention include occupational therapy. Tobar provides a detailed review of the role of occupational therapy in delirium prevention in critically ill patients and provides a vision for future research in this area[44]. Environmental improvements, including minimizing noise and light at night and promoting sleep consolidation, can also help prevent delirium onset[45]. Reducing physical activity limitations is also important to allow patients to move early; physical activity restriction triples the odds of delirium[46].

Pharmacological approaches to delirium prevention include the use of melatonin to preventing delirium. Melatonin improves sleep quality and increases sedation levels, preventing and reducing delirium incidence. However, melatonin does not reduce delirium duration in patients who already have delirium[47]. In response to sleep problems, it is also necessary to determine in the clinic whether the problem is organic or functional; organic diseases, such as heart and respiratory disease, can also include sleep problems. In functional sleep problems, adjusting the sleep rhythm can help prevent delirium occurrence. In addition, patients with sleep problems caused by fear of surgery and changes in the sleep environment are considered functional. The use of melatonin in such cases improves sleep rhythm and prevents delirium [48]. The use of other sleep-improving drugs, such as ramelteon, for delirium prevention has also been studied[49].

Antipsychotic use for delirium prevention remains highly controversial. A randomized placebo-controlled study showed that haloperidol had a preventive effect in elderly hip surgery patients at risk of delirium[50]. Numerous studies have been conducted on haloperidol for delirium prevention[51,52]. A risperidone trial for delirium prevention in postoperative cardiac patients found that postoperative delirium incidence was significantly lower in the 1 mg risperidone group than in the placebo group (11.1% *vs* 31.7%, $P = 0.009$)[53]. A review of studies concluded that antipsychotic medication use was not related to delirium duration, severity, or place of care and that there was high heterogeneity among studies[54]. Second-generation antipsychotics are more effective than placebo in preventing delirium onset; however, delirium severity was not reduced in patients receiving prophylactic antipsychotics[55].

IDENTIFICATION OF OVERLAPPING SYMPTOMS

Clinical manifestations

The clinical manifestations of delirium are complex and vary, and they are described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, as altered attention, significantly different from the basal level and accompanied by changes in consciousness, cognitive decline, and sleep rhythm disturbances[56]. Delirium has a rapid onset and appearance of symptoms, duration of several hours or days, and a fluctuating nature. For ease of memory, the diagnostic criteria for delirium have been described more simply as A (attention and awareness), disturbances in attention and awareness; B (short period, hours or days), developing over a short period, usually hours or days; C (cognitive deficit), cognitive decline; D (disturbances in A and C), other cognitive deficits that interfere with A and C judgment, such as a complete coma state, are excluded; and E (exposure to medical conditions or drugs), exposure factors, such as surgery and medications.

The diagnostic process consisted of two basic steps. First, a bedside patient assessment was performed to determine the level of attention and arousal and the presence of other cognitive deficits, psychotic features, or mental status abnormalities. Second, the patient's baseline attention and consciousness status were determined by accompanying relatives or caregivers to obtain evidence of acute change.

Assessment methods

After the initial diagnosis, the patient must be further evaluated to obtain more details, including features such as delusions, hallucinations, and mood changes. These details are very important and affect the patient's subsequent treatment or management plan.

Neuropsychological scales: More than 50 assessment tool scales have been developed, with varying conditions of use, mainly including use when delirium first appears or is suspected, when monitoring delirium in hospitalized patients on a regular daily basis, during brief screening, during detailed symptom documentation and neuropsychological assessment, and when assessing delirium severity[57]. Table 2 shows the commonly used neuropsychological scale of delirium assessment.

Ancillary investigations: Delirium assessment should also consider its precipitating factors; therefore, detailed ancillary examinations such as blood, computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalography (EEG) should be performed. In routine blood parameters, the mean red blood cell volume and aspartate aminotransferase can be delirium predictors in trauma patients[58]. Routine blood tests should corroborate the patient's medical history and clinical features. In addition, some cases of delirium are caused by primary central nervous system disease. Specific brain tests, such as CT or MRI, EEG, lumbar puncture, and antibody testing for autoimmune encephalitis, are selectively performed in such cases. However, it is not reasonable to perform CT in all patients with delirium. A study that included 1653 patients showed that only 11% of patients had positive CT findings, with cerebral hemorrhage being the most common cause of delirium[59]. MRI showed that reduced cerebral blood flow, oxygenation, and abnormal glucose uptake might be associated with delirium, including a high white matter signal in the brain[60].

Differential diagnosis and superimposed symptoms

Although there are similarities in clinical manifestations between the delirium and dementia subtype, including fluctuating cognitive decline exhibited by dementia with Lewy body (DLB), visual hallucinations or delusions exhibited by DLB and Parkinson's disease dementia, and attention deficit in severe Alzheimer's disease (AD), all are similar to delirium presentation. However, there are also significant differences: in terms of the mode of onset, delirium is acute and dementia is slowly progressive; concerning duration, delirium usually lasts for a few hours or days, while dementia lasts for a long time; and there is decreased arousal in delirium and that in dementia remains relatively intact.

Previous studies have shown that symptoms such as dementia and depression sometimes appear in parallel with delirium, leading to poor prognosis and high in-hospital mortality and readmission rates. Identifying delirium superimposed dementia (DSD) is important for timely treatment. Patients with dementia who suddenly present with symptoms such as irritability, unexplained falls, resistance or reluctance to communicate with caregivers, drowsiness, and hallucinations need to be closely monitored for DSD and promptly treated symptomatically[61]. Delirium and depression are very common neuropsychiatric syndromes in the elderly, and accurate condition determination is necessary for providing the best treatment plan. However, the considerable clinical overlap of symptoms makes proper identification difficult, leading to adverse medical outcomes, such as clarifying whether the patient's mood disorder is a manifestation of delirium or depression or the comorbidity or primary stage before implementing therapeutic measures [62].

CLINICAL MEASURES AFTER DELIRIUM ONSET

The best management strategy is a multifaceted intervention focused on treating precipitating illnesses, reviewing medication regimens, managing distress, mitigating comorbidities, and maintaining environmental comfort. Clinical measures are divided into non-pharmacologic, non-antipsychotic, and antipsychotic measures.

Table 2 Common delirium assessment scales

Name	Time (min)	Application	Sensitivity (%)	Specificity (%)	Rigorous training	Suitable for examining DSD
Confusion Assessment Method (CAM)[92,93]	3-10	No ICU	46-94	63-100	Yes	Yes
The 4A's test (4AT)[94]	< 2	No ICU	86-100	65-82	No	Yes
The 12-item Stanford Proxy Test for Delirium (S-PTD)[95]	5	No ICU	80	90	No	No
Richmond Agitation Screening Scale (RASS)[96,97]	1	Delirium has just started	65-75	82-90	No	Yes
The Recognizing Acute Delirium As part of your Routine (RADAR)[98]	< 1	Delirium has just started	73	67	No	Yes
Confusion Assessment Method for ICU (CAM-ICU)[99]	< 5	ICU	28-100	53-99	Yes	Yes
Intensive Care Delirium Screening Checklist (ICDSC)[100]	7-10	ICU	73-97	69-97	Yes	No
Delirium Triage Screen (DTS)[101]	< 1	Screening	82	96.1	No	No
Ultra Brief 2 Item Screener (UB-2)[102, 103]	< 1	Screening	93	64	No	No
Simple Question for Easy Evaluation of Consciousness (SQEEC)[104]	< 1	Screening	93	81	No	No
Delirium Rating Scale revised-98 (DRS-R98)[105]	20	Detailed neuropsychological assessment	57-93	82-98	Yes	Yes
Memorial Delirium Assessment Scale (MDAS)[106]	7-10	Detailed neuropsychological assessment	64-82	75-100	Yes	No
CAM Severity (CAM-S)[107]	5	Detailed neuropsychological assessment	NR	NR	No	No

NR: Not reported; ICU: Intensive care unit; DSD: Delirium superimposed dementia.

Non-pharmacologic measures

Non-pharmacological measures are recognized to be effective in dealing with delirium. The intervention protocols vary among studies and mainly include orientation, cognitive stimulation, early activity, non-pharmacological sleep improvement, sensory impairment correction, identification and intervention of potential controllable risk factors or postoperative complications, pain management, gastrointestinal function improvement, supplemental nutrition, and enhancing oxygen delivery.

The Hospital Elder Life Program (HELP) is a systematic non-pharmacological intervention program[63]. According to the British Institute for Health Care Excellence guidelines for preventing, diagnosing, and managing delirium, HELP added entries for coping with hypoxia, infection, pain, and constipation[64].

After delirium onset, non-pharmacological approaches are an indispensable way. Summarily, the main points are ABCDEF: A (assessing, preventing, and managing pain); B (both spontaneous awakening and spontaneous breathing trials), promoting spontaneous awakening and breathing; C (choice of analgesia and sedation), selection of a reasonable analgesic regimen; D (delirium assessment, management, and prevention), delirium pre-assessment, management, and prevention; E (early mobility), early activity; and F (family engagement), family involvement[65].

The primary treatment of delirium is still focused on identifying and managing potential triggers. In practice, the choice of clinical measures will vary according to patient-specific situations. It is crucial to summarize treatment strategies that minimize delirium severity and duration.

Non-antipsychotic measures

Antiepileptic drugs: Valproic acid is effective in both case reports and retrospective cohort studies for delirium treatment [66,67]. Valproic acid can be administered orally or intravenously and is effective in patients with delirium associated with alcohol withdrawal, a history of traumatic brain injury, or mood disorders. Valproic acid should be avoided in pregnant women and patients with significant hepatic or pancreatic dysfunction, active bleeding, or low platelet counts. Before starting valproic acid treatment, patients should have their blood counts and liver enzyme levels checked and monitored.

Alpha-2 agonists: Dexmedetomidine, an alpha-2 agonist, effectively reduces agitation associated with delirium, decreases CNS sympathetic activity, and indirectly reduces the risk of drug combinations by reducing the use of other delirium medications. A national study showed that dexmedetomidine effectively controlled delirium in postoperative patients

other than those undergoing cardiac surgery[68].

Melatonin: The effects of melatonin on delirium have been described previously. Case and retrospective studies have shown that ramelteon helps treat delirium, especially active delirium[69,70]. Melatonin is well-tolerated and safe in the population. The role of melatonin and its receptor agonists in delirium treatment deserves to be studied in-depth. It can enhance sleep consolidation and maintain a good sleep-wake cycle in delirious patients.

Vitamin B1: Nutritional deficiencies, especially vitamin B deficiencies, are associated with delirium[71]. Vitamin B1 deficiency can lead to a range of changes in mental status, including Wernicke's encephalopathy (a triad of nystagmus, oculomotor paralysis, and altered mental status), Korsakoff's syndrome (irreversible memory impairment, usually the result of untreated Wernicke's encephalopathy), and delirium.

Antipsychotic measures

Although no medications have been approved by the United States Food and Drug Administration (FDA) specifically for treating delirium, antipsychotic medications are often used as first-line medications to respond to and manage patients when non-pharmacologic measures are insufficient to control or improve symptoms. However, antipsychotic use for delirium treatment remains controversial. Several studies have shown that the benefits of using antipsychotic medications outweigh the risks for patients, particularly in improving agitation and psychotic symptoms[72,73]. For the control of delirium incidence, duration, severity, length of hospital stay, and mortality, antipsychotic use does not achieve satisfactory results[54].

Obvious psychotic symptoms, such as hallucinations and delusions, can be controlled using antipsychotic drugs. Antipsychotic medications' sedative effect can effectively resolve agitation in patients with delirium. For the core delirium symptoms, including decreased attention and cognition, there is no evidence that antipsychotic medications are effective. More importantly, patients should be carefully monitored for adverse reactions and side effects after antipsychotic medication use.

The choice of medication should be based on the actual clinical situation of the patient to choose the option that maximizes the benefit[74]. For patients with severe circadian rhythm and perceptual disturbances, sedative antipsychotics, such as quetiapine, can be selected for nighttime use; for patients with overexcited delirium, haloperidol can be selected and administered intravenously or intramuscularly for those who cannot tolerate oral administration; for delirium in patients with PD or DLB, quetiapine is preferable because first-generation antipsychotics can aggravate motor symptoms in patients with PD; if these two groups of patients need parenteral medication, olanzapine or ziprasidone can be selected to be administered intramuscularly at minimal doses; olanzapine and risperidone can be selected for patients who cannot swallow; and olanzapine can be used to exert its antiemetic effect when delirium occurs in cancer patients.

Drug dosage was initially administered at the lowest dose and frequency, as assessed by symptom severity[74]. In addition, three major critical values need to be monitored: QTc prolongation (increased risk of sudden death from ventricular tachycardia), extrapyramidal symptoms, and all-cause death in patients with dementia. QTc prolongation is usually associated with antipsychotic use. An investigational study conducted by Pfizer for FDA comparing the QTc interval before and after the use of the maximum daily dose found QTc prolongation ranging from 4.7 ms (haloperidol) to 20.3 ms (ziprasidone)[75]. Patients with delirium should have an electrocardiogram before receiving antipsychotic medication and ensure no significant QTc prolongation interval during treatment. Patients with delirium receiving antipsychotics must also be monitored for extrapyramidal symptoms, such as inability to sit still, rigidity, and dystonia, which can exacerbate emotional disturbances and cause them to change their treatment plans.

DISCUSSION

The complexity and variability delirium symptoms make determining treatment plans more difficult. Patients with delirium are usually admitted to the hospital from the emergency room. The key to treatment is to quickly identify the cause and promptly remove susceptibility factors and triggers, while supporting with symptomatic treatment, maintaining electrolyte balance, and supplementing nutrition. It is also important to prevent complications such as falls, aspiration (aspiration pneumonia), decubitus ulcers, and deep vein thrombosis. A thorough physical examination, detailed history taking, and necessary ancillary laboratory tests are important for detecting the primary cause. Common factors that cause delirium, including infection, cerebrovascular factors, pharmacological factors, surgical anesthesia, and major physical diseases of the heart, lungs, liver, and kidneys, were excluded. Symptomatic treatment of delirium caused by such factors effectively improves symptoms.

In addition, numerous somatic diseases can cause mild edema in the brain cells, leading to transient consciousness impairment. From this perspective, non-pharmacological measures, although not directly therapeutic, can facilitate and accelerate recovery. These include psychotherapy (suggestion), environmental measures (placement of familiar objects in the room), soft lighting (light therapy), and restraint (use during the attack period to avoid accidents). Subsequently, after correcting the primary physical illness, the brain function was restored and delirium symptoms disappeared.

A primary method to prevent delirium is to simply shorten hospitalization, as much as possible[76,77]. Unfamiliar environment, and lack of separation between day and night and disorientation are frequent during admission are also major causes for delirium. Notably, early discharge is beneficial to patient recovery when their health condition is accurately assessed[78].

The following aspects should be noted for the more controversial use of psychiatric drugs. First, psychiatric medications (first or second generation) usually inhibit a person's cognitive-behavioral activity. The principle is to use them as little as possible and for as short a time as possible. Second, psychiatric drugs were selected in the following cases: (1) The patient was agitated; (2) There were many hallucinatory delusions; (3) Behavioral disturbances; (4) Sleeplessness at night; and (5) Non-cooperation and poor compliance with general supportive therapy. Third, ECG should be checked regularly during treatment with psychiatric drugs, and QT interval changes should be closely monitored. When the following two factors are encountered: (1) Prolonged QT interval suggested by ECG on admission; and (2) electrolyte disturbance, psychiatric drugs should be used with caution. The safety of valium drugs is higher than that of psychiatric medications. When the two factors mentioned above improve after clinical treatment, psychiatric drugs or tranquilizer administration should be considered. When using valium, attention should be paid to whether the patient has obstructive respiratory diseases, myasthenia gravis, and other valium contraindications. Protective restraint is more appropriate when both psychotropic drugs and tranquilizers are at greater risk of use. Fourth, clinical readiness to assess the benefit of patients with psychotropic medications: (1) From the patient's perspective, the improvement of psychiatric-behavioral symptoms; and (2) from the caregiver's perspective, there is usually a significant psychosomatic burden of care for patients with delirium, and the severity of the caregiving burden directly affects the quality of patient care.

Patients usually recover within 7-10 d, with a few recovering in 2-4 wk, rarely developing into chronic delirium. Delirium has also been reported to have long-term effects on cognition[24]. The cognitive impairment that occurs after delirium onset in ICU patients is similar to that caused by moderate traumatic brain injury. Moreover, delirium can lead to more severe dementia in AD patients in addition to original dementia, and the risk of dementia development after delirium onset in older adults is eight times higher than that in normal older adults.

CONCLUSION

Summary and outlook

This study comprehensively discussed the latest national and international research perspectives on delirium in terms of risk factors, preventive interventions, overlapping symptoms, and clinical and specific measures to clinically deal with delirium in real-world situations.

Key points

This paper reviews the whole delirium process and its latest research progress in risk factors, preventive interventions, identification of superimposed symptoms, and clinical measures to provide a comprehensive and systematic account of delirium and present the latest medical information. This article helps readers improve understanding of delirium and helps clinicians quickly identify and take timely therapeutic measures to address the various delirium subtypes that occur in the clinic setting. This is to ensure that patients can be treated as aggressively as possible.

FOOTNOTES

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Diagnostic and prognostic implications of non-high-density lipoprotein cholesterol and homocysteine levels for cognitive impairment in thalamic infarction

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Abstract

BACKGROUND

Patients with thalamic infarction experience abnormal blockages of multinucleated vessels, affecting the body and thereby the thalamus. Most patients with thalamic infarction have an adverse prognosis, which seriously affects their safety. Therefore, it is essential to analyze the independent risk factors that influence the prognosis of patients with thalamic infarction and develop corresponding preventive measures.

AIM

To explore the effect of non-high-density lipoprotein cholesterol (non-HDL-C) and Homocysteine (Hcy) levels in cognitive impairment in thalamic infarction.

METHODS

From March 2019 to March 2022, 80 patients with thalamic infarction were divided into a group with cognitive impairment [Montreal Cognitive Assessment (MoCA) score < 26; 35 patients] and a group with normal cognitive function (MoCA score of 26-30; 45 patients) according to the MoCA score. In addition, 50 healthy people in the same period were selected as the control group. A correlation between the non-HDL-C and Hcy levels and the MoCA score and receiver operating characteristic curve was observed, and the serum non-HDL-C and Hcy levels were analyzed for the diagnosis of cognitive impairment in patients with thalamic infarction. According to the Modified Rankin Scale (MRS) score, 80 patients with thalamic infarction were divided into a good prognosis group (MRS score ≤ 2) and a poor prognosis group (MRS score >2).

RESULTS

The non-HDL-C and Hcy levels were significantly higher in the group with cognitive impairment than in the group with normal cognitive function ($P < 0.05$).

There was no significant difference in the non-HDL-C level between the control group and the group with normal cognitive function ($P > 0.05$). The MoCA scores of the group with cognitive impairment were significantly lower than those of the group with normal cognitive function and the control group ($P < 0.05$). There was a significant difference between the control group and the group with normal cognitive function ($P < 0.05$). The non-HDL-C and Hcy levels were correlated with the MoCA score ($P < 0.05$), cognitive impairment [areas under the curve (AUC) = 0.709, 95% confidence interval (95%CI): 0.599-0.816], the non-HDL-C level, and could predict cognitive impairment in patients with thalamic infarction (AUC = 0.738, 95%CI: 0.618-0.859). Hcy combined with non-HDL-C levels can predict cognitive impairment in patients with thalamic infarction (AUC = 0.769, 95%CI: 0.721-0.895).

RESULTS

There were 50 patients in the good prognosis group and 30 patients in the poor prognosis group. Compared with the good prognosis group, in the poor prognosis group, the National Institutes of Health Stroke Scale (NIHSS) score, non-HDL-C level, Hcy level, large-area cerebral infarction, atrial fibrillation, and activated partial prothrombin time were statistically significant ($P < 0.05$). The non-HDL-C level, the Hcy level, the NIHSS score, extensive cerebral serum, and atrial fibrillation may all be independent risk factors for poor prognosis in patients with thalamic infarction ($P < 0.05$).

CONCLUSION

Non-HDL-C and Hcy levels are positively correlated with cognitive impairment in patients with thalamic infarction. Non-HDL-C and Hcy levels can be used in the diagnosis of cognitive impairment in patients with thalamic infarction, and the combined detection effect is better. The main factors affecting the prognosis of patients with thalamic infarction are the non-HDL-C level, the Hcy level, the NIHSS score, large-area cerebral infarction, and atrial fibrillation. Clinically, corresponding preventive measures can be formulated based on the above factors to prevent poor prognosis and reduce mortality.

Key Words: Thalamic infarction; Cognitive impairment; Non-high-density lipoprotein cholesterol; High homocysteine level; Diagnostic value; Prognosis; Influencing factors; Correlation

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Core Tip: This study explored the diagnostic and prognostic implications of non-high-density lipoprotein cholesterol (non-HDL-C) and Homocysteine (Hcy) levels for cognitive impairment in patients with thalamic infarction. Both non-HDL-C and Hcy levels were found to be useful for the diagnosis of cognitive dysfunction in patients with thalamic infarction, with their combined detection being more effective. In addition, clinical precautions can be formulated based on their levels to prevent poor prognosis and reduce mortality.

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INTRODUCTION

The organization and structure of the thalamus is extremely complex, such as the medial nuclear group and the former nuclear group. In patients with thalamic infarction, an abnormal blocking phenomenon occurs in the blood vessels of multiple nuclei, affecting the body and thereby the thalamus. The majority of patients are mainly characterized by dementia, aphasia and stubborn sexual behavior and insomnia, aggravating the degree of the thalamic infarction, which can lead to cognitive impairment[1]. One study reported that abnormal homocysteine (Hcy) levels led to changes in hippocampal signaling and neuroplasticity in mice[2]. Therefore, abnormal Hcy levels are believed to be related to cognitive impairment in patients with thalamic infarction. Non-high-density lipoprotein cholesterol (non-HDL-C), which mainly contains low density lipoprotein (LDL), intermediate density lipoprotein and chylomicron, is calculated by subtracting HDL from total cholesterol (TC). Other studies have also reported that there is a relationship between non-HDL-C levels and cognitive impairment[3]. For example, in the study of Weaver *et al*[4], non-HDL-C levels were positively correlated with cognitive impairment in patients with lacunar cerebral infarction. As the non-HDL-C level increased in patients with lacunar cerebral infarction, the degree of cognitive impairment increased. However, whether the same occurs in patients with thalamic infarction needs to be further explored. Hcy and non-HDL-C levels are related to cognitive impairment due to disease to a certain extent. Whether Hcy and non-HDL-C levels can be used in the diagnosis of cognitive dysfunction in patients with thalamic infarction is worth exploring. Most patients with thalamic infarction have a poor prognosis, and their safety is seriously affected. The analysis of independent risk factors, especially

Hcy levels, for the prognosis of patients with thalamic infarction and the formulation of relevant prevention measures have important meaning for improving the prognosis of these patients, and whether non-HDL-C level changes can predict the prognosis of patients with thalamic infarction is worth studying. Therefore, this study mainly evaluated the use of Hcy and non-HDL-C levels in the diagnosis of cognitive impairment in patients with thalamic infarction, as well as the influencing factors of poor prognosis to provide a reference for the clinical development of preventive measures to improve the prognosis of these patients. At the same time, the efficient diagnosis of cognitive impairment in patients with thalamic infarction provides a reference for improving the prognosis of these patients, which is of great significance.

MATERIALS AND METHODS

General information

From March 2019 to March 2022, 80 patients diagnosed with thalamic infarction were selected and divided into a group with cognitive dysfunction [Montreal Cognitive Assessment (MoCA) score < 26, 35 patients] and a group with normal cognitive function (MoCA score of 26-30, 45 patients) according to the MoCA score. In addition, 50 healthy people in the same period were included as the control group. There was no significant difference in sex or age among the three groups ($P > 0.05$, see Table 1). After 2 years of follow-up, the prognosis of the 80 patients was evaluated. The selected patients with thalamic infarction were divided into a good prognosis group (Modified Rankin Scale (MRS) score ≤ 2 points) and a poor prognosis group (MRS score > 2 points) according to the MRS score. The inclusion criteria were as follows: patients who were diagnosed by computed tomography or magnetic resonance imaging; patients who met the Cerebrovascular Disease Conference criteria for the diagnosis of thalamic infarction[5]; patients who were admitted within 72 h of onset; and patients who had not taken diuretic drugs or antibiotics within 1 mo after admission. The exclusion criteria were as follows: Patients with dysfunction of the heart, lungs or other organs; patients with malignant tumors or other diseases; patients with immune system diseases; and patients with severe disorders of consciousness. Details are shown in Table 1.

Research methods

Non-HDL-C and Hcy level detection: After fasting for 12 h, venous blood was drawn from the elbow at 6 am the next day, and the serum levels of TC and HDL-cholesterol were detected by an automatic biochemical analyzer. Non-HDL-C levels were calculated as follows: TC-HDL-C.

First, blank wells, standard wells and sample wells were set, corresponding to the addition of standard solution or the solution to be tested, and incubated. Then, biotinylated antibody and enzyme conjugate working solution was added. Next, the liquid in the wells was cleared, and the substrate solution was added.

MoCA score[6]: An MoCA score of less than 26 indicates cognitive impairment, and an MoCA score of 26-30 indicates normal cognition. The evaluation content mainly includes the following aspects: Visuospatial executive ability, naming, attention, language ability, abstraction, delayed recall and orientation. According to the MoCA score, patients with thalamic infarction were divided into a group with normal cognitive function and a group with cognitive dysfunction.

MRS score[7]: An MRS score ≤ 2 indicated a good prognosis, and an MRS score of 3-6 indicated a poor prognosis; a higher score indicated a worse prognosis. An MRS score of 0 indicated that no symptoms were present, and scores of 1 to 5 points indicated different degrees of disability; the higher the score was, the more severe the disability was. A score of 6 indicates patient death. For clinical symptoms, a score of 1 point indicated mild but not significant disability. Scores of two and three points indicated moderate disability, but with the ability to walk alone. A score of 4 points indicated a moderately severe disability, with the inability to walk independently, and a score of 5 points indicated a severe disability and the complete inability to take care of oneself. According to the MRS score, patients with thalamic infarction were divided into a good prognosis group and a poor prognosis group.

National Institutes of Health Stroke Scale score[8]: The Stroke Scale developed by the National Institutes of Health[9] includes level of consciousness, level of consciousness questioning, level of consciousness commands, and optimal gaze. The total score ranges from 0 to 42, with higher scores indicating more severe neurological damage.

Outcome measures: The diagnosis of cognitive impairment was determined and the prognosis of patients with thalamic infarction was predicted using non-HDL-C and Hcy levels. MoCA score, onset time, National Institutes of Health Stroke Scale (NIHSS) score, and activated partial prothrombin time (APTT) were also used as outcome measures.

Statistical methods

SPSS 26.0 and GraphPad Prism software were used to analyze the data. Data on the non-HDL-c level, Hcy level, MoCA score, onset time, NIHSS score, APTT, *etc.* were collected. The chi square test, LSD test (homogeneity of variance test $P < 0.05$) and Tamheeni test (homogeneity of variance test $P < 0.05$) were performed in the three groups (group with cognitive impairment, control group and group with normal cognitive function), and χ^2/t tests were performed in the two groups (good prognosis group and poor prognosis group) (all were in line with a normal distribution). The *t* test was used for quantitative data and the χ^2 test was used for qualitative data. The correlation between non-HDL-C and Hcy levels and the MoCA score was analyzed by Pearson correlation analysis. The diagnostic value of non-HDL-C and Hcy levels in patients with thalamic infarction was analyzed by receiver operating characteristic (ROC) curve analysis. The independent risk factors for poor prognosis in patients with thalamic infarction were analyzed by logistic regression analysis. Logistic regression analysis was used to analyze independent risk factors for a poor prognosis in patients with

Table 1 Observed differences in basic data

Group	The number of cases	Male/female	Age (yr)
The control group	50	24/26	63.11 ± 6.45
Cognitively normal group	45	25/15	64.87 ± 6.69
Cognitive impairment group	35	27/13	64.76 ± 6.45
χ^2/F/*P* value	-	3.657/0.073	1.482/0.187

thalamic infarction.

RESULTS

Non-HDL-C and Hcy levels in the diagnosis of cognitive impairment in patients with thalamic infarction

Differences in non-HDL-C and Hcy levels in each group: The non-HDL-C and Hcy levels in the group with cognitive impairment were significantly higher than those in the group with normal cognitive function and the control group ($P < 0.05$), and there was no significant difference between the control group and the group with normal cognitive function ($P > 0.05$). Details are shown in Table 2.

Table 2 Differences in non-HDL-C and Hcy levels in each group (X ± S)

Group	The number of cases	Non-HDL-C (tendency/L)	Hcy (mol/L)
The control group	50	3.11 ± 0.52	11.66 ± 0.71
Cognitively normal group	45	3.24 ± 0.54	23.22 ± 3.68
Cognitive impairment group	35	3.98 ± 0.87[1,2]	30.34 ± 4.72[1,2]
F/P value	-	6.393/0.000	25.417/0.000

[1]$P < 0.05$ compared with the control group.
[2]$P < 0.05$ compared with the group with normal cognitive function.
Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine.

Observation of differences in MoCA scores: The MoCA score of the group with cognitive impairment was significantly lower than those of the group with normal cognitive function and the control group ($P < 0.05$), and there was no significant difference between the control group and the group with normal cognitive function (P>0.05). Details are shown in Table 3.

Correlation analysis of non-HDL-C and Hcy levels with MoCA scores: Non-HDL-C and Hcy levels were positively correlated with the MoCA score ($P < 0.05$). See Table 4 for details.

ROC curve analysis of the use of serum non-HDL-C and Hcy levels in the diagnosis of cognitive impairment in patients with thalamic infarction: The areas under the curve (AUC) of Hcy levels in predicting cognitive impairment in patients with thalamic infarction was 0.709 [95% confidence interval (95%CI): 0.599-0.816]. The AUC of non-HDL-C levels in predicting cognitive impairment in patients with thalamic infarction was 0.738 (95%CI: 0.618-0.859). The AUC of Hcy combined with non-HDL-C levels in predicting cognitive impairment in patients with thalamic infarction was 0.769 (95%CI: 0.721-0.895). See Table 5 and Figure 1 for details.

The prognostic value of non-HDL-C and Hcy levels in patients with thalamic infarction

Differences in the clinical characteristics of patients with thalamic infarction in the good and poor prognosis groups: There were 50 patients in the good prognosis group and 30 patients in the poor prognosis group. There were significant differences in NIHSS scores, non-HDL-C levels, Hcy levels, and rates of massive cerebral infarction, atrial fibrillation, and APTT between the poor prognosis group and the good prognosis group ($P < 0.05$). Details are shown in Table 6.

Multivariate logistic regression analysis of the influencing factors of a poor prognosis in patients with thalamic infarction: Non-HDL-C levels, Hcy levels, NIHSS scores and atrial fibrillation may be independent risk factors for poor prognosis in patients with thalamic infarction ($P < 0.05$). Details are shown in Table 7.

Table 3 Differences in Montreal Cognitive Assessment scores (X ± S)

Group	The number of cases	Visuospatial executive ability	Named	Attention	Language ability	Abstract	Delayed recall	Directional	Total score
The control group	50	3.12 ± 1.04	2.80± 0.45	5.84 ± 0.37	2.88 ± 0.33	1.78 ± 0.51	3.10 ± 1.23	5.86 ± 0.35	25.46 ± 2.41
Cognitively normal group	45	4.39 ± 0.72	2.79 ± 0.39	5.69 ± 0.41	22.98 ± 0.09	1.87 ± 0.15	3.62 ± 0.91	5.63 ± 0.36	26.98 ± 1.20
Cognitive impairment group	35	1.73 ± 1.25	1.62 ± 0.98	12.31 ± 1.09	2.61 ± 0.50	1.43 ± 0.89	2.16 ± 1.01	4.69 ± 1.66	17.13 ± 4.53[1,2]
F/P value	-	11.962/0.000	7.309/0.000	28.304/0.000	329.283/0.000	3.263/0.002	6.784/0.000	341.597/0.000	13.992/0.000

[1]$P < 0.05$ compared with the control group.
[2]$P < 0.05$ compared with the group with normal cognitive function.

DISCUSSION

This study first analyzed the use of non-HDL-C and Hcy levels in the diagnosis of cognitive impairment in patients with thalamic infarction; 80 patients with thalamic infarction were selected as the research object, and the MoCA score was used to evaluate the degree of cognitive impairment in the patients. Patients with thalamic infarction were divided into a group with cognitive impairment and a group with normal cognitive function, and medical healthy people were included as controls. The non-HDL-C and Hcy levels in the group with cognitive impairment were significantly higher than those in the group with normal cognitive function and the control group. At the same time, the MoCA scores of the group with cognitive impairment were higher than the scores of each subgroup. In addition, the scores of the group with normal cognitive function and the control group were higher. The higher the MoCA score was, the more normal a patient's cognitive function. The above results showed that there was a certain relationship between the non-HDL-C and Hcy levels and cognitive function in patients. The higher the non-HDL-C and Hcy levels were, the lower the cognitive function of patients. Pearson correlation analysis also showed that the non-HDL-C and Hcy levels were correlated with the MoCA score. The higher the non-HDL-C and Hcy levels were, the lower the MoCA score, indicating more severe cognitive impairment in patients. The results of this study have also been confirmed in a number of studies, such as the study by Fu *et al*[10]. The study found that the Hcy level was associated with cognitive dysfunction in patients with cerebral infarction. The relationship between non-HDL-C and Hcy levels and cognitive dysfunction was further analyzed. The increase in Hcy levels resulted in an abnormal decrease in the vasodilation response, and the activity of CO synthetase was affected; this increased the degree of endothelial injury, further leading to abnormal endothelial function, and promoting the shedding of a large number of endothelial cells. In turn, the formation of arteriosclerosis was affected, ultimately leading to cognitive dysfunction[11]. In addition, an abnormal increase in non-HDL-C levels in the body leads to cognitive dysfunction, which may be mainly related to atherosclerosis. The increased levels of non-HDL-C and LDL-C in the body may lead to the development of atherosclerosis, which may lead to arterial stenosis, increased plaque formation and changes in hemodynamics. An abnormal blood supply in the thalamus may lead to some structural dysfunction, such as in the hippocampus and adjacent tissues, eventually leading to cognitive dysfunction[12].

The ROC curve was further used to analyze the diagnostic efficacy of non-HDL-C and Hcy levels for cognitive impairment in patients with thalamic infarction. The results showed that the combination of non-HDL-C and Hcy levels had higher diagnostic efficacy, which suggested that the combined measurement of non-HDL-C and Hcy levels could be considered to improve the diagnostic efficacy in the diagnosis of cognitive dysfunction in patients with thalamic

Table 4 Correlation analysis of non-high-density lipoprotein cholesterol and Homocysteine levels and the Montreal Cognitive Assessment score

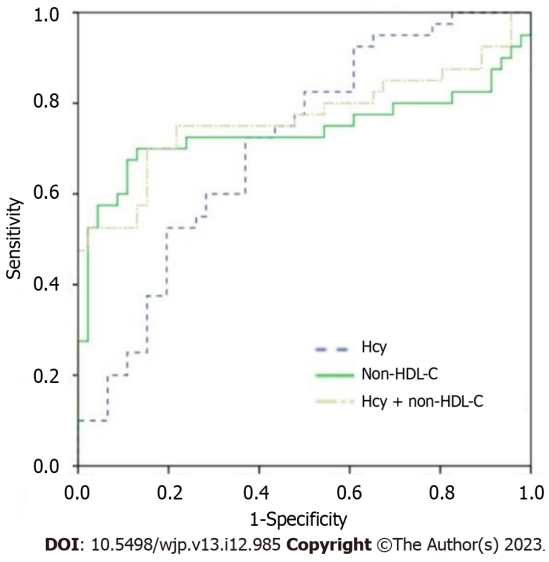
Project	Hcy		non-HDL-C	
	r value	*P* value	*r* value	*P* value
Viewspace/execution	0.292	0.003	0.233	0.000
Named	0.478	0.000	0.487	0.004
Attention	0.658	0.002	0.622	0.000
Language ability	0.451	0.000	0.422	0.002
Abstract	0.302	0.001	0.368	0.000
Delay memories	0.367	0.000	0.308	0.002
Directional	0.685	0.003	0.676	0.001
MoCA scores	0.703	0.000	0.705	0.000

Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine; MoCA: Montreal Cognitive Assessment.

Table 5 Receiver operating characteristic curve analysis of serum non-high-density lipoprotein cholesterol and Homocysteine levels for the diagnosis of cognitive impairment in patients with thalamic infarction

Variable	The critical value	AUC	Sensitivity	Specificity	95%CI	About an index
Hcy (μmol/L)	22.540	0.709	0.724	0.630	0.599-0.816	0.354
Non-HDL-C (tendency/L)	1.351	0.738	0.701	0.870	0.618-0.859	0.571
Hcy in combination with non-HDL-C	-	0.769	0.758	0.889	0.721-0.895	0.647

AUC: areas under the curve; Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine.



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Figure 1 Receiver operating characteristic curve analysis of serum non-high-density lipoprotein cholesterol and Homocysteine levels in the diagnosis of cognitive impairment in patients with thalamic infarction. Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine.

infarction.

To analyze the independent risk factors for poor prognosis in patients with thalamic infarction, the patients were divided into groups according to their follow-up results, and the MRS score was used to evaluate the prognosis of the patients. The results showed that there were 50 patients with a good prognosis and 30 patients with a poor prognosis. There were statistically significant differences in the NIHSS score, non-HDL-C level, Hcy level, and rates of massive

Table 6 Differences in clinical characteristics between patients with thalamic infarction in the good and poor prognosis groups

Project	Good prognosis group (*n* = 50)	Poor prognosis group (*n* = 30)	χ^2/t	*P* value
Age (yr)	65.12 ± 6.74	64.13 ± 10.07	0.527	0.600
Men	32 (64.00)	20 (66.67)	0.059	0.809
Time of onset (h)	20.39 ± 3.21	20.42 ± 3.19	0.041	0.968
Smoking history	26 (52.00)	16 (53.33)	0.013	0.908
The history of drinking	24 (48.00)	13 (43.33)	0.164	0.685
Hypertension	24 (48.00)	18 (60.00)	1.083	0.298
Diabetes	14 (28.00)	9 (30.00)	0.037	0.848
CHD	8 (16.00)	4 (13.33)	0.105	0.746
NIHSS score	14.52 ± 5.43	17.91 ± 5.78	2.639	0.010
Non-HDL-C (tendency/L)	3.08 ± 0.46	3.79 ± 0.57	6.103	0.000
Hcy (μmol/L)	14.54 ± 0.78	27.51 ± 4.08	21.909	0.000
Massive cerebral infarction	13 (26.00)	15 (50.00)	4.747	0.029
Atrial fibrillation	6 (12.00)	9 (30.00)	3.988	0.046
APTT (1 S)	31.55 ± 3.45	33.43 ± 4.32	2.144	0.035

APTT: Activated partial prothrombin time; CHD: Coronary heart disease; Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine; NIHSS: National Institutes of Health Stroke Scale.

Table 7 Multivariate logistic regression analysis of influencing factors of a poor prognosis in patients with thalamic infarction

Variable	OR	95%CI	Wald	*P* value
Atrial fibrillation	0.232	0.068-0.768	5.701	0.016
Non-HDL-C	1.753	1.243-2.477	10.187	0.001
Hcy	1.051	1.006-1.096	5.323	0.020
APTT	1.127	1.003-1.186	4.116	0.077
NIHSS score	1.091	1.004-1.268	4.134	0.012

95%CI: 95% confidence interval; APTT: Activated partial prothrombin time; Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine; NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio.

cerebral infarction, atrial fibrillation and APTT between the good prognosis group and the poor prognosis group. Logistic regression analysis showed that there were statistically significant differences in the NIHSS score, non-HDL-C level, Hcy level, and rates of atrial fibrillation and APTT between the groups. The non-HDL-C level, Hcy level, NIHSS score, massive cerebral infarction, and atrial fibrillation may be independent risk factors for poor prognosis in patients with thalamic infarction. Hcy levels can lead to an inflammatory response and abnormal endothelial cell function and promote thrombosis, which is one of the influencing factors for poor prognosis in patients with thalamic infarction[13]. Non-HDL-C levels can lead to the development of atherosclerosis in the body and increase the risk of cognitive dysfunction. The NIHSS score is a protective factor in patients with thalamic infarction. The NIHSS score can predict the recovery of patients' neurological function and be used to further judge patient prognosis[14]. Atrial fibrillation is a common arrhythmia and is also a risk factor in patients with thalamic infarction. Due to the generation of atrial fibrillation, cardiac structural abnormalities, hemodynamics, and the micro embolus synthetic quantity are increased, cerebral perfusion and cerebral hypoperfusion are reduced, differences in the ventricular rate occur and the heart rate, cerebral blood flow, and neuronal energy is affected. The nerve fiber and amyloid beta protein levels are reduced, which leads to disorders of speech speed and thinking expression and ultimately affects the prognosis of patients with thalamic infarction[15]. Clinically, for patients with thalamic infarction, relevant preventive measures can be formulated according to the above influencing factors, such as anticoagulant drug therapy to reduce the incidence of atrial fibrillation[16]. The NIHSS was used to evaluate neurological function in patients. Appropriate supplementation with folic acid or other antipsychotic drugs can reduce the Hcy level to a certain extent[17], and the prophylactic use of statins can reduce the non-HDL-C level [18].

CONCLUSION

In conclusion, non-HDL-C and Hcy levels are positively correlated with cognitive impairment in patients with thalamic infarction. Non-HDL-C and Hcy levels can be used for the diagnosis of cognitive impairment in patients with thalamic infarction, and the combined detection effect is better. The prognostic factors of patients with thalamic infarction mainly include the non-HDL-C level, Hcy level, NIHSS score, and rates of large area cerebral infarction and atrial fibrillation. Clinically, corresponding preventive measures can be formulated according to the above factors to prevent poor prognosis and reduce mortality. However, there are some shortcomings in this study. The sample source is biased, the sample size is small, and thalamic infarction is not a common disease because non-HDL-C and Hcy levels may also be affected by other factors. Only the combination of non-HDL-C and Hcy levels in the diagnosis of cognitive dysfunction in patients indicates great deficiencies. This only indicates that non-HDL-C and Hcy levels can be detected simultaneously in the auxiliary diagnosis of cognitive dysfunction in patients with thalamic infarction to improve the diagnostic efficiency.

ARTICLE HIGHLIGHTS

Research background

In patients with thalamic infarction, the blood vessels of multiple nuclei are abnormally blocked, affecting the body and thus the thalamus. Abnormal Homocysteine (Hcy) levels are believed to be related to cognitive impairment in patients with thalamic infarction. Meanwhile, there is a positive correlation between non-high-density lipoprotein cholesterol (non-HDL-C) levels and cognitive impairment in lacunar cerebral infarction.

Research motivation

The analysis of the impact of independent risk factors, especially Hcy levels, on the prognosis of patients with thalamic infarction and the formulation of relevant prevention measures carries great clinical implications for improving patient outcomes. In addition, the value of changes in non-HDL-C levels in predicting the prognosis of patients with thalamic infarction deserves investigation.

Research objectives

To provide a reference for the clinical development of preventive measures to improve the prognosis of patients with thalamic infarction and to efficiently diagnose cognitive impairment in such patients.

Research methods

Eighty patients with thalamic infarction were included and divided into a group with cognitive impairment [Montreal Cognitive Assessment (MoCA) score: < 26] and a group without (MoCA score: 26-30), depending on their MoCA scores. In addition, 50 concurrent healthy controls were selected as a control group. Correlations of the non-HDL-C and Hcy levels with the MoCA score and receiver operating characteristic curve were observed. Serum non-HDL-C and Hcy levels were further analyzed. Furthermore, patients were grouped as a good prognosis group [Modified Rankin Scale (MRS) score: ≤ 2] and a poor prognosis group (MRS score: > 2) according to the MRS score, and the clinical characteristics were comparatively analyzed.

Research results

There was a certain relationship between non-HDL-C and Hcy levels and cognitive function in patients, with higher non-HDL-C and Hcy levels indicating worse cognitive function of patients. Pearson correlation analysis also identified an association between non-HDL-C and Hcy levels and MoCA scores. Specifically, the higher the levels of non-HDL-C and Hcy, the lower the MoCA score, indicating more severe cognitive impairment in patients.

Research conclusions

Non-HDL-C and Hcy levels are positively correlated with cognitive impairment in patients with thalamic infarction, indicating their potential to diagnose cognitive impairment in such patients. In addition, their combined detection contributes to higher diagnostic efficacy.

Research perspectives

Simultaneous detection of non-HDL-C and Hcy levels can assist in the diagnosis of cognitive dysfunction in patients with thalamic infarction, which is of great clinical significance for improving the prognosis of these patients.

FOOTNOTES

Author contributions: Zhu SY and Zhang H conceived and designed the study; Zhu SY and Ge W guided the study; Zhu SY and Zhang H collected the clinical date; Zhu SY and Zhang H analyzed the data; All authors drafted and revised the manuscript.

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ORIGINAL ARTICLE

Case Control Study

Brain-derived neurotrophic factor, sex hormones and cognitive decline in male patients with schizophrenia receiving continuous antipsychotic therapy

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Abstract

BACKGROUND

There are systematic differences in clinical features between women and men with schizophrenia (SCZ). The regulation of sex hormones may play a potential role in abnormal neurodevelopment in SCZ. Brain-derived neurotrophic factor (BDNF) and sex hormones have complex interacting actions that contribute to the etiology of SCZ.

AIM

To investigate the influence of BDNF and sex hormones on cognition and clinical symptomatology in chronic antipsychotic-treated male SCZ patients.

METHODS

The serum levels of follicle-stimulating hormone, luteinizing hormone (LH), estradiol (E2), progesterone, testosterone (T), prolactin (PRL) and BDNF were compared between chronic antipsychotic-treated male (CATM) patients with SCZ (n = 120) and healthy controls (n = 120). The Positive and Negative Syndrome Scale was used to quantify SCZ symptoms, while neuropsychological tests were used to assess cognition. Neuropsychological tests, such as the Digit Cancellation Test (DCT), Semantic Verbal Fluency (SVF), Spatial Span Test (SS), Paced Auditory Serial Addition Test (PASAT), Trail Making Task (TMT-A), and Block Design Test (BDT), were used to assess executive functions (BDT), attention (DCT, TMT-A), memory (SS, PASAT), and verbal proficiency (SVF).

RESULTS

Although E2 levels were significantly lower in the patient group compared to the

healthy controls, T, PRL, and LH levels were all significantly higher. Additionally, the analysis revealed that across the entire sample, there were positive correlations between E2 Levels and BDNF levels as well as BDNF levels and the digital cancellation time. In CATM patients with SCZ, a significant correlation between the negative symptoms score and PRL levels was observed.

CONCLUSION
Sex hormones and BDNF levels may also be linked to cognitive function in patients with chronic SCZ.

Key Words: Brain-derived neurotrophic factor; Clinical symptoms; Cognitive function; Schizophrenia; Sex hormones

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Core Tip: Brain-derived neurotrophic factor (BDNF) and sex hormones are known to be involved to the psychopathology of schizophrenia (SCZ). However, the influence of BDNF and sex hormones on cognition and symptoms in chronic antipsychotic-treated male (CATM) SCZ patients have yet to be investigated. Testosterone, prolactin (PRL) and luteinizing hormone were significantly higher in the patient group than in the healthy controls while estradiol (E2) levels were significantly lower. Analysis also identified positive correlations between E2 levels and BDNF levels, and BDNF levels and the digital cancellation time, in the whole sample. we found significant correlations between PRL levels and negative symptoms score in CATM patients with SCZ.

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INTRODUCTION

It has been proved that there are differences in schizophrenia (SCZ) clinical side effects between females and males[1]. In SCZ, gender differences may play a significant role in the factors that mediate schizophrenic expression[2]. The current study hypothesizes that sex hormones alter the manifestation of symptoms, either directly or indirectly, and account for many of the observed gender differences[3]. The organizational and activational effects of sex hormones on SCZ have received a lot of critical attention[4]. During a crucial period in the fetus's life, organizational effects have a permanent impact on the developing brain. Evidence recommends that adjustments to sex hormones might be related to the neurodevelopmental etiology of SCZ[5]. The actuating impacts are the immediate impact of circulating chemicals. When hormone levels rise, the impact will appear, and when hormone levels fall, the impact will become weaker. Both luteinizing hormone (LH) and testosterone (T) play a role in puberty by promoting the expansion of white matter in the frontal and temporal connections[6]. It is important to note that the regions of the brain that are most affected by adolescent gonadal hormones are also the regions of the brain that are most relevant to the pathophysiology of SCZ[7]. Recent research indicates that T and masculinity predict hippocampus or cerebellum volumes that are typically larger in men[8], whereas estradiol (E2) levels were associated with bilateral insula resting-state functional connectivity in girls[9]. Adolescent hormonal changes may activate genes that regulate normal neurodevelopment, leading to an increase in connectivity and a decrease in gray matter[10].

T has genomic and non-genomic impacts on the cerebrum through androgen receptors, and is involved in hippocampal CA1 neuron morphology[11]. It has been established that estrogen plays a role in cognitive processes such as memory, learning, and mood regulation[12]. Studies in rats have shown that progesterone (P), a neurosteroid, has numerous impacts on cognition, for example, upgrading learning and memory, advancing nerve development and myelination[13].

Sex hormones and brain-derived neurotrophic factor (BDNF) have been linked to cognitive function in an increasing number of studies. For example, a new investigation on ovariectomized rodents showed that E2 essentially expanded spatial learning and memory by increasing 17 β-E2 and BDNF levels in the hippocampus[14]. The BDNF pathway plays a role in the protective effects of estrogen. Additionally, P interferes with estrogen's protective effect under certain conditions[15]. In grown-up male rodents, treatment with T and BDNF intuitively affected androgen receptor articulation [16] as well as dendritic length[17]. According to our previous research, patients with chronic SCZ who suffer from attention and spatial memory impairments have elevated serum T levels[18]. However, there are currently insufficient systematic studies on the interplay between BDNF and follicle-stimulating hormone (FSH), LH, E2, P, T, and prolactin (PRL) in chronic antipsychotic-treated male (CATM) patients.

We hypothesize that neurotrophic factors mediate cognitive decline in male patients with chronic SCZ *via* hormones. This article focuses on the following issues: (1) Whether patients with chronic SCZ have altered levels of BDNF and sex hormones (including FSH, LH, E2, P, T, and PRL); (2) Whether there is a connection between BDNF and sex hormone levels; and (3) Whether the communication between BDNF and sex hormones is involved in the clinical symptoms and

cognition of SCZ patients.

MATERIALS AND METHODS

Participants

This was a case-control study, and the sample size calculation method was as follows: = 0.05, β = 0.20, Meant = 0.25, and Meanc = 0.21; the sample size calculation was input into the Biostatistics website (www.cnstat.org/samplesize/12/), and the difference between the two sets of means was compared, n = 200 (cases). If the maximum number of lost cases was considered to be 20%, then the total number of cases in both groups should be: 200 + 200 0.2 ≈ 240 (cases), nt = 120 (cases), nc = 120 (cases) and power = 0.8036.

A total of 120 CATM patients with SCZ from the Affiliated WuTaiShan Hospital of the Medical College of Yangzhou University (Yangzhou, China) were recruited between February 2018 and July 2019. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, these patients fulfilled the criteria for SCZ. In addition, 120 healthy males were included as control subjects. The controls were matched by age and education with the SCZ group. All the controls were in good physical health and had no mental illness. Table 1 depicts the demographic characteristics of the patient group and the healthy control group. Participants in this study must have taken antipsychotic medication for at least a year. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Subjects were excluded if they had a history of substance abuse or dependence, neurological diseases, or serious psychiatric comorbidities.

The WuTaiShan Hospital Ethics Committee approved the study (approval No. 2018-011), and written informed consent was provided by each participant.

Hormone assay

Serum samples were centrifuged (3000 rpm for 10 min) and then stored at -80°C. Sex hormone levels (FSH, LH, E2, P, T, PRL) were estimated using an Entrance immunoassay analyzer and the manufacturer's reagents (Beckman Coulter Inc., Brea, CA, United States). After that, an enzyme-linked immunosorbent assay (Emax Immunoassay System kit) was used to measure the concentration of BDNF (Promega, Madison, WI, United States) according to the instructions of the manufacturer.

Neurocognitive assessments

A neuropsychological battery of cognitive tests, such as the Digit Cancellation Test (DCT), Semantic Verbal Fluency (SVF), Spatial Span Test (SS), Paced Auditory Serial Addition Test (PASAT), Trail Making Task (TMT-A), and Block Design Test (BDT), were used to assess cognitive performance.

The followings were evaluated by the neurocognitive battery: Executive functions: Executive functions were evaluated using the BDT. Maintaining focus and attention: Attention was evaluated using the DCT and TMT-A. Memory: The SS and PASAT were used to measure memory. Verbal proficiency: Verbal fluency was assessed by the SVF test.

Statistical analysis

SPSS 17.0 was used for the statistical analysis (SPSS Inc., Chicago, IL, United States). We first compared the qualities and mental execution between the controls and patients, and then compared the BDNF and sex hormone levels of patients and controls using the independent samples t-test. The next step was to investigate the connections between BDNF levels and cognitive function in the entire sample (n = 240) and between sex hormone levels and BDNF levels. Pearson's product moment correlation was used to investigate the connections between the patient group's PANSS scores and sex hormone levels. After taking into account any potential confounders, the relationship between sex hormone levels and PANSS scores, BDNF levels, and cognitive function was modeled using multiple linear regression. The Bonferroni correction was used to adjust for multiple comparisons. The significance level was set at $P < 0.05$.

RESULTS

Demographic data, sex hormones, BDNF, and cognitive performances in patients and healthy controls

The characteristics and clinical data of 120 CATM patients with SCZ and 120 controls are presented in Table 1. There were significant differences in body mass index (BMI) between patients and controls ($P < 0.001$). The patient group had significantly higher levels of LH ($P < 0.05$), T ($P < 0.05$), and PRL ($P < 0.001$) than the controls (both $P < 0.001$), and significantly lower levels of BDNF and E2 than the controls (both $P < 0.001$). The patients performed worse in all mental subscales (all $P < 0.001$). These data are shown in Table 2.

Interrelationships of sex hormones and BDNF in all subjects

In all subjects (n = 240), LH, E2, T, and PRL ($P < 0.05$) were all fundamentally connected to BDNF levels before adjustment of confounding factors (age, schooling, smoking, BMI). Only the relationships between BDNF levels and LH, E2, and PRL remained significant ($P < 0.05$) after confounding factors were removed. The relationship between E2 and BDNF remained statistically significant after Bonferroni correction ($P < 0.01$). These data are shown in Table 3.

Table 1 Demographic characteristics, clinical data, brain-derived neurotrophic factor, and sex hormones in chronic antipsychotic-treated male patients with schizophrenia and healthy controls (mean ± SD)

Variable	CATM patients (*n* = 120)	Healthy controls (*n* = 120)	F or χ^2 (*P* value)
Age (yr)	51.0 ± 10.3	52.2 ± 6.4	27.4 (0.28)
Education (years)	9.2 ± 3.0	9.1 ± 2.8	0.8 (0.62)
Smokers (%)	60.8	65.9	0.6 (0.4)
BMI (kg/m^2)	25.7 ± 3.4	24.0 ± 2.2	33.5 (< 0.001)
BDNF (ng/mL)	2.5 ± 1.6	9.7 ± 3.2	35.5 (0.00)
FSH (ng/mL)	8.6 ± 6.7	9.0 ± 6.6	0.1 (0.67)
LH (ng/mL)	6.7 ± 3.3	4.9 ± 2.6	1.6 (0.00)
E2 (ng/mL)	40.5 ± 17.1	56.2 ± 24.3	4.5 (0.00)
P (ng/mL)	0.8 ± 0.3	0.8 ± 0.4	0.2 (0.84)
T (ng/mL)	4.8 ± 1.8	4.0 ± 1.2	2.4 (0.01)
PRL (ng/mL)	25.4 ± 22.4	10.6 ± 5.5	24.1 (0.00)
Age of onset (yr)	22.9 ± 5.8		
Duration of illness (yr)	28.0 ± 9.3		
PANSS score			
Positive symptoms	11.3 ± 4.9		
Negative symptoms	20.1 ± 10.0		
General psychopathology	31.2 ± 9.0		
Total score	62.6 ± 20.2		

BDNF: Brain-derived neurotrophic factor; CATM: Chronic antipsychotic-treated male; BMI: Body mass index; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; T: Testosterone; PRL: Prolactin; PANSS: Positive and Negative Syndrome Scale.

Table 2 Comparison of cognitive scores between chronic antipsychotic-treated male schizophrenia patients and healthy controls

Cognitive index	CATM patients	Controls	F (*P* value)	MD (95%CI)
DCT	304.1 ± 215.0	130.8 ± 43.3	50.8 (< 0.001)	173.2 (124.0 to 222.4)
SVF	16.0 ± 7.8	27.6 ± 7.9	0.0 (< 0.001)	-11.6 (-8.7 to -14.5)
SS	11.6 ± 4.2	16.4 ± 4.2	0.1 (< 0.001)	-4.7 (-3.4 to -6.1)
TMT-A	101.3 ± 57.9	50.0 ± 21.7	26.5 (< 0.001)	51.3 (35.6 to 67.0)
BDT	17.1 ± 9.0	31.8 ± 8.8	0.2 (< 0.001)	-14.7 (-11.6 to -17.8)
PASAT correct	19.8 ± 10.5	34.0 ± 10.2	0.0 (< 0.001)	-14.1 (-9.5 to -18.7)
PASAT try	23.9 ± 11.0	36.9 ± 10.7	0.4 (<0.001)	13.0 (-8.2 to 17.8)

95%CI: 95% confidence interval; DCT: Digit Cancellation Test; SVF: Semantic Verbal Fluency; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task; BDT: Block Design Test.

Relationships between BDNF and cognitive functions in all subjects

In all subjects, the DCT, class familiarity, SS, TMT-A, block design, and PASAT were all fundamentally connected to BDNF levels prior to adjustment of confounding factors (all $P < 0.001$). Only the relationships between BDNF levels and the DCT, category fluency, TMT-A, and block design remained significant ($P < 0.05$) after confounding factors were taken into account. The relationship between DCT and BDNF levels remained significant after Bonferroni correction ($P < 0.0023$). These data are shown in Table 4.

Relationships between PRL levels and psychotic symptoms in CATM patients

In CATM patients with SCZ, significant association between PRL levels and the negative side effects score ($r = 0.196$, $P <$

Table 3 Correlations between sex hormones and brain-derived neurotrophic factor levels in all subjects[1]

	BDNF			
	r	*P* value[2]	*P* value[3]	*P* value[4]
FSH (ng/mL)	0.068	0.467	0.638	NS
LH (ng/mL)	-0.256	0.007	0.011	NS
E2 (ng/mL)	0.343	< 0.001	0.001	S.
P (ng/mL)	0.074	0.459	0.173	NS
T (ng/mL)	-0.215	0.032	0.055	NS
PRL (ng/mL)	-0.267	0.004	0.04	NS

[1]Pearson product moment.
[2]Before adjusting for confounding factors.
[3]After adjusting for confounding factors (body mass index).
[4]Bonferroni correction was applied (a new = 0.05/5 = 0.01).
NS: Not significant; S.: Significant; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; T: Testosterone; PRL: Prolactin.

Table 4 Correlations between brain-derived neurotrophic factor levels and cognitive function in all subjects[1]

	BDNF			
	r	*P* value[2]	*P* value[3]	*P* value[4]
DCT	-0.376	< 0.001	0.0019	NS
Category fluency	0.539	< 0.001	0.022	NS
SS	0.307	< 0.001	0.398	NS
TMT-A	-0.516	< 0.001	0.010	NS
Block design	0.557	< 0.001	0.015	NS
PASAT correct	0.442	< 0.001	0.404	NS
PASAT try	0.405	< 0.001	0.201	NS

[1]Pearson product moment.
[2]Before adjusting for confounding factors.
[3]After adjusting for confounding factors (body mass index).
[4]Bonferroni correction was applied (a new = 0.05/7 = 0.007).
NS: Not significant; DCT: Digit Cancellation Test; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task.

0.05) and the score for general psychopathology was found (r = 0.181, P < 0.05). The relationship between PRL levels and general psychopathology or negative factors remained significant (P < 0.05) after adjusting for confounding factors. As shown in Table 5, only the relationship between PRL levels and the negative factors remained significant after the Bonferroni correction (P < 0.017).

DISCUSSION

The CATM group's elevated levels of LH, PRL, and T, in addition to their decreased levels of E2, were examined in depth for the first time in this study in comparison to the controls. One of the major findings in this study was that E2 Levels and BDNF levels, as well as BDNF levels and the DCT, were correlated in all subjects. Even after Bonferroni correction and adjusting for confounding factors, these correlations remained significant.

Previous studies have shown that in men, LH and T seem to have a role in advancing the development of white matter [6,10]. As gender differences play a significant role in SCZ, hormones may play a role in the pathophysiology of SCZ. In the initial period of SCZ in men, higher T levels in puberty and youth, show that T might be related to the initiation of psychosis in patients[19]. Recently, an ever-increasing number of studies have focused on dehydroepiandrosterone (DHEA)/T in addition to standard antipsychotic treatment in relation to the side effects of SCZ[20]. These studies demonstrated that patients with SCZ experiencing negative, depressive, and anxiety symptoms could benefit from DHEA augmentation as a treatment. However, we found that CATM patients with SCZ had T levels higher than those in the

Table 5 Relationships between prolactin levels and psychotic symptoms in patients[1]

	Positive symptoms score				Negative symptoms score				General psychopathology score			
	r	*P* value[2]	*P* value[3]	*P* value[4]	*r*	*P* value[2]	*P* value[3]	*P* value[4]	*r*	*P* value[2]	*P* value[3]	*P* value[4]
PRL	0.152	0.098	0.254	NS	0.196	0.032	0.011	S.	0.181	0.048	0.030	NS

[1]Pearson product moment.
[2]Before adjusting for confounding factors.
[3]After adjusting for confounding factors (body mass index).
[4]Bonferroni correction was applied (a new = 0.05/3 = 0.017).
NS: Not significant; S.: Significant; DCT: Digit Cancellation Test; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task.

controls, but that there was no correlation between this increase and psychopathology. It was demonstrated that decreasing levels of LH reduced short-term episodic memory loss in an SCZ model treated with phencyclidine[21]. We found that the LH levels in the CATM patients with SCZ were higher than those in controls, even though there was no relationship between this increment and mental capability.

It has been hypothesized for a considerable amount of time that the blocking effect of antipsychotic medications on dopamine D2 receptors is the cause of the elevated PRL levels associated with psychotic symptoms. PRL levels were found to be elevated in CATM patients with SCZ in the current study. However, unlike a previous study that investigated patients with chronic SCZ, we found no link between elevated PRL and impaired cognitive function[22]. Hyperprolactinemia was most significantly associated with executive function, working memory, and processing speed in a previous study of prolactinoma patients[23]. In addition, it was discovered that a decrease in the volume of gray matter in the frontal cortex and hippocampus was correlated with PRL concentration. In the future, the connection between PRL levels and cortical thickness and hippocampal base volume in patients with ongoing SCZ should be examined to determine the connection between hyperprolactinemia and diminished mental capability.

Research focusing on the connection between PRL levels and the side effects of SCZ has been primarily conducted in male patients; however, no consistent conclusion has been reached. Positive symptoms, delusions, and speech incoherence are all negatively correlated with PRL levels, according to some researchers[24]. On the other hand, one study found a correlation between positive symptoms in schizophrenic patients and elevated PRL levels[25]. Another review showed that PRL levels were significantly connected with negative side effects[26]. One study found no link between psychopathology and PRL levels[27]. In previous studies[25,28], we found that higher PRL levels and negative side effects were connected.

The "estrogen hypothesis" has been used for more than three decades to explain how estrogen protects the brain. E2 and selective estrogen receptor modulators are helpful adjunctive treatments for patients with SCZ[29]. Our study found that CATM patients with SCZ had lower levels of the protective hormone E2 than normal male controls. This finding is consistent with the preceding hypotheses. It was found that BDNF gene expression can be controlled by estrogen[30]. Indeed, even after two measurement revisions, this study found a huge direct connection between E2 and BDNF, which is consistent with previous investigations.

The higher incidence of SCZ in men and the earlier age of onset may be partially explained by T[31]. Our current findings were consistent with those of another study[32] in which SCZ cases had significantly higher T levels and significantly lower BDNF levels compared to controls. A previous study with a small sample size found a significant

correlation between low T levels and penile-related symptoms in men taking antipsychotics and a trend in hyperprolactinemia was associated with low T[33]. Antipsychotics frequently result in hyperprolactinemia, which can affect the measurement of other gonadal hormone levels[34]. It should be noted that antipsychotics such as clozapine and aripiprazole are less likely to cause hyperprolactinemia.

Even though these conclusions are not consistent, more and more researchers are focusing on the connection between SCZ with impaired cognitive function and abnormal serum BDNF levels[35,36]. However, a recent study found that first-episode and drug-naive SCZ patients had significantly higher BDNF serum levels and better Repeatable Battery for the Assessment of Neuropsychological Status scores[37]. In a previous study, we found that the improvement in clinical symptoms was linked to higher BDNF levels in schizophrenic patients[38]. Similarly, we observed that the level of BDNF in SCZ patients was lower than that in controls and that there was a positive relationship between BDNF levels and mental capability. We also found critical and positive relationships between E2 and BDNF levels, and between BDNF levels and the DCT. Even after Bonferroni correction and adjusting for confounding factors, these correlations remained significant. Rashidy-Pour *et al*[14] in 2019 demonstrated that E2 significantly increased spatial learning and memory by increasing 17-E2 and BDNF levels in the hippocampus of ovariectomized rats. The BDNF pathway is responsible for estrogen's neuroprotective effects[16]. However, we found no correlation between BDNF levels and clinical symptoms. This necessitates further investigation into the reasons for this finding.

The limitations of this study require consideration. The lack of confirmation regarding the consistency of the markers in the central nervous system and peripheral blood is the primary limitation of this study. As the biomarkers were only measured once in this case-control study, the study was constrained by the lack of longitudinal comparisons. Thirdly, the study did not determine how antipsychotic medication affected BDNF and gonadal hormone levels.

CONCLUSION

In conclusion, CATM patients with SCZ showed lower levels of BDNF and E2 and elevated levels of LH, T, and PRL compared to controls. In all cognitive subscales, we found that CATM patients with SCZ performed significantly worse. In CATM patients with SCZ, we also found a marked relationship between PRL levels and the negative side effects score. Sex hormones and BDNF levels may also be linked to cognitive function. With the exception of PRL and negative symptoms, this case-control study only found positive correlations across the entire sample. As a result, our findings ought to be regarded as preliminary.

ARTICLE HIGHLIGHTS

Research background

Due to gender differences in the clinical manifestations of schizophrenia (SCZ), this study assumes that sex hormones directly or indirectly alter the clinical manifestations of SCZ.

Research motivation

An increasing number of studies have shown that sex hormones act through brain derived neurotrophic factors (BDNF), which can also affect the expression of sex hormone receptors.

Research objectives

The purpose of this study is to explore the significant impact of the interaction between BDNF and sex hormones on the clinical manifestations and cognitive function of chronic antipsychotic-treated male (CATM) SCZ patients.

Research methods

We used a cross-sectional case-control study method to collect blood from both normal control and CATM SCZ patients for testing BDNF and sex hormone levels, as well as cognitive function in both groups.

Research results

We found a significant decrease in estradiol (E2) levels in the patient group, and a significant correlation between prolactin levels and negative symptom scores. In the entire sample, there is a positive correlation between E2 level, BDNF level, and the Digit Cancellation Test (reflecting attention function).

Research conclusions

Compared with the normal control group, there were changes in the levels of BDNF and sex hormones in the patient group. The levels of sex hormones in the patient group are related to negative symptoms.

Research perspectives

The interaction between BDNF and sex hormones may be involved in negative symptom expression and cognitive impairment in chronic male SCZ patients.

FOOTNOTES

Co-corresponding authors: Qiu-Fang Jia and Xiao-Bin Zhang.

Author contributions: Li J and Zhang XB designed the study and manuscript preparation; Li J and Xiao WH recruited subjects, collected clinical data, laboratory samples, and cognitive assessment and did preliminary data analysis; Ye F and Tang XW assisted in the symptoms of schizophrenia assessment and data analysis; Jia QF did literature search, final analysis of the data, and prepared the final manuscript; All authors contributed to manuscript preparation and approved its final version. Qiu-Fang Jia and Xiao-Bin Zhang contributed equally to this work as co-corresponding authors. The reasons for designating Qiu-Fang Jia and Xiao-Bin Zhang as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Qiu-Fang Jia and Xiao-Bin Zhang contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Qiu-Fang Jia and Xiao-Bin Zhang as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORIGINAL ARTICLE

Case Control Study

Haplotype analysis of long-chain non-coding RNA NONHSAT102891 promoter polymorphisms and depression in Chinese individuals: A case-control association study

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Abstract

BACKGROUND

Our previous study reported that the single-nucleotide polymorphism (SNP) rs155979 GC in the promoter region of long-chain non-coding RNA (lncRNA) NONHSAT102891 affects depression susceptibility in a Chinese population.

AIM

To explored associations of two SNPs and haplotypes in the lncRNA NONHSAT102891 promoter region with depression susceptibility in Chinese population.

METHODS

This this case-control association study was approved by the Ethics Committee of Chengdu Medical College (approval number: 201815). Patient diagnosis was based on DSM-IV criteria. We selected a total of 480 patients with depression and 329 healthy controls with no history of psychopathology, and performed genotyping of two SNPs by extracting peripheral venous blood samples from the subjects. The function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes was detected by dual-luciferase reporter assays of human embryonic kidney 293T transfected cells.

RESULTS

Stratified analysis of clinical and genotypic characteristics of our cohort showed that the degree of mild depressive episodes associated with the rs6230 TC/CC genotype increased by 1.59 times [TC/CC *vs* TT: odds ratio (OR) = 1.59, 95%

confidence interval (CI): 1.08-2.35, P = 0.019]. The haploid analysis revealed linkage disequilibrium between rs3792747 and rs6230, and the double SNP CG haplotype was more common in the control group compared to case group, indicating that this haplotype significantly reduced the risk of depression (C/G *vs* T/A: OR = 0.42, 95%CI: 0.21-0.83, P = 0.01). There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P > 0.05), indicating that the double SNP haplotype has no transcriptional activity.

CONCLUSION

The rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter may be related to a reduced risk of depression in the Han Chinese population.

Key Words: Long-chain non-coding RNA NONHSAT102891; Depression; Susceptibility; Single-nucleotide polymorphisms; Haplotype; Transcriptional activity

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Core Tip: Depression has risen to the top of the global burden of non-fatal diseases. Recently, emerging evidence supports long-chain non-coding RNA (lncRNA) may be involved in the occurrence and development of depression, and may serve as potential diagnostic and prognostic markers. Our previous study showed lncRNA NONHSAT102891 rs155979 GC affects depression susceptibility; this study genotyped 480 depression patients and 329 healthy controls for the two single-nucleotide polymorphisms and made dual-luciferase reporter assays to explore and elucidate the function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes. We found the rs6230 and rs3792747 CG haplotypes may reduce the risk of depression, which expanded our knowledge about this disease.

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INTRODUCTION

Depression is a highly heterogeneous and multifactorial mental illness with symptoms spanning domains of emotion and behavior, including changes in mood, anhedonia, sleep, and psychomotor activity[1]. With an estimated 5% of adults worldwide suffering from depression each year, depression has risen to the top of the global burden of non-fatal diseases [2]. In the post-coronavirus disease 2019 era, the global burden of mental disorders has become heavier, and has brought greater challenges to the diagnosis and treatment of depression. In China, health service utilization for depressive disorders is very low, with only 9.2% of depressed patients receiving adequate treatment[3]. Depression can also occur in patients with other underlying diseases, including Alzheimer's disease, stroke, multiple sclerosis and cardiovascular disease[4-6].

Long-chain non-coding RNAs (lncRNAs) are the most abundant class of ncRNAs in the human genome. Characteristically, lncRNAs are more than 200 bp in length and do not encode a protein, but may interact with DNA, RNA or protein molecules at multiple levels (epigenetic, transcriptional and post-transcriptional) to control the expression of related genes and participate in many biological processes, especially differentiation and development[7,8]. Approximately 40% of the lncRNAs in the mammalian genome are expressed in the brain[9]. LncRNAs are involved in regulation of neuronal function and play an important role in neuropsychiatric diseases. Through alternative splicing or binding to NRG1, v-erb-a erythroblastic leukemia viral oncogene homolog 4 gene expression inhibits downstream neurons, reduces the release of the neurotransmitter gamma-aminobutyric acid, and has negative effects on brain functions, such as cognition and working memory, in addition to an association with an increased risk of depression and schizophrenia[10-12]. LncRNAGm^{2}694 destroys endoplasmic reticulum homeostasis, significantly reduces expression of the A-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor on the postsynaptic membrane of neurons, reduces the excitatory synaptic transmission function of neurons, increases stress susceptibility in mice, and mediates the pathogenesis of depression[13]. In addition, some single-nucleotide polymorphisms (SNPs) in lncRNAs are associated with the risk of depression. A human-specific Alu insertion polymorphism (rs70959274) in the 5' flanking region of the lncRNA LINC01360 is in strong linkage disequilibrium with the major depression SNP rs12129573[14]. Identifying functional variants of non-coding SNPs is essential for understanding the molecular mechanism and biological basis of depression [15]. Changes in lncRNAs can be detected in cerebrospinal fluid as well as the circulatory system and brain, therefore, providing important prospects for use as biomarkers for disease identification or risk prediction. These biomarkers can also be employed to provide new insights into the genetic structure and biological etiology of neuropsychiatric diseases.

The term "haplotype" refers to several closely linked SNPs that determine the same trait on the same chromosome or in a certain region, either as two loci or the entire chromosome. CONVERGE consortium conducted sparse whole-genome sequencing on Chinese female patients with recurrent major depression and found two depression-related mutations, both located on chromosome 10, one near SIRT1, and the other in an intron of the *LHPP* gene[16]. LncRNA NONHSA T102891, which is located on chromosome 5 (CHR5): 95768987-95770845, has a transcript length of 1860 bp. A recent genome-wide association study (GWAS) revealed five genomic domains on CHR5 that were significantly associated with depression. The underlying background of these regions also includes LINC00461, MEF2C, and LOC101927421[17]. In human tissues, lncRNA NONHSAT 102891 is expressed in the thyroid, brain, adrenal glands and placenta[18]. Downregulated expression of lncRNA NONHSAT102891 in peripheral blood mononuclear cells of major depressive disorder (MDD) patients has been explored previously[19]. Furthermore, changes in the expression of NONHSA T102891 may be a potential non-invasive biomarker for the diagnosis of MDD[20].

In our previous study, we investigated the diagnostic and differential diagnostic value of lncRNA NONHSAT10289 (rs155979, rs3762983, rs3762984 and rs102891) SNPs in severe depression[21]. Because the polymorphism of a single locus in a gene often cannot reveal its true association with disease, haplotype analysis of multiple loci has become an effective means to find complex disease genes. Therefore, in this study, we compared the expression of the other two SNP (rs6230 and rs3792747) in the lncRNA NONHSAT102891 promoter region in patients with depression to further assess the association of lncRNANONHSAT102891 promoter SNPs and/or haplotypes with risk of depression in a Chinese population and to determine the functional correlation of risk haplotypes.

MATERIALS AND METHODS

Study subjects

From March 2018 to December 2019, a total of 480 patients with depression and 329 healthy individuals from three hospitals in China (Sichuan Provincial People's Hospital, Jining Psychiatric Hospital and Yunnan Provincial Mental Health Center) were recruited to the case and control groups, respectively. All participants were Han Chinese adults. The study protocol was approved by the Ethics Committee of Chengdu Medical College (No. 201815). All participants provided written informed consent. Patient diagnosis was based on the DSM-IV criteria, and the symptom severity was scored using the 24-item Hamilton Depression Rating Scale (HAMD-24). Patients with neurological diseases or other mental disorders, acute or chronic infections, thyroid dysfunction, being pregnant, or breastfeeding at the time of the study were excluded. Control subjects were volunteers with no history of self-reported mental illnesses and who participated in physical examination in the research hospitals. The following clinical data were collected from medical records: Age, sex, age of onset, HAMD-24 score, pulse rate, degree of depression, family history, suicide attempt/behavior and first episode.

The average age of the healthy control group (105 males and 224 females) was 44.0 ± 16.9 years. The case and control groups were matched according to sex, age and place of residence. Details of the participants can be found in our previous report[21].

SNP selection

The UCSC Genome Browser was used to explore SNPs of the lncRNA NONHSAT102891 promoter region (3-kb region upstream of the transcription initiation site)[22]. The SNPs rs6230 and rs3792747 were selected as loci with minor allele frequencies > 10% in the Asian population to study their correlation with depression susceptibility and clinical characteristics in a Han Chinese population.

Genotyping

Genomic DNA was extracted from peripheral venous blood samples using the whole blood genomic DNA extraction kit [Shenggong Bioengineering (Shanghai) Co., Ltd.]. The concentration of the DNA was determined as a measure of the quality by using a NanoDrop 2000/2000C [Thermo Fisher (China) Co., Ltd.]. The lncRNA NONHSAT102891 promoter region containing the rs6230 and rs3792747 polymorphisms was amplified by two-step polymerase chain reaction (PCR) to prepare an Illumina compatible library using the following primer sequences: rs3792747-F: *5'-TCAATGCAGCAGCATCATCAGATCCAAG-3'*, rs3792747-R: *5'-CGGGCAAAGTTATGAAGCTTGGACT-3'*, rs6230-F: *5'-GATCCCAGCAAACAGTTCCT-3'*; rs6230-R: *5'-CCAGCCAGAATGGAAATGAG-3'*.

The first-step PCR (25 μL reaction volume) amplification was performed under the following reaction conditions: 98 ℃, 3 min; 98 ℃, 30 s; 50 ℃, 30 s; 72 ℃ 30 s; 98 ℃, 30 s; 66 ℃ 30 s; 25 cycles for 30 s at 72 ℃, and 72 ℃ for 5 min. Using the first-step PCR product as the template, the Illumina sequencing library was obtained by the second round of PCR (30 μL reaction volume) amplification performed under the following reaction conditions: 98 ℃, 5 min; 94 ℃, 30 s; 55 ℃, 20 s; 5 cycles of 72 ℃, 30 s. The sizes of the two PCR products were confirmed by 1% agarose gel electrophoresis and then recovered using AMPure XP magnetic beads. Equal amounts of the two PCR products were then mixed and sequenced using HiSeqXTen platform (Illumina, San Diego, CA, United States).

Construction of luciferase reporter gene plasmids

The DNA fragments containing the haplotypes of the lncRNA NONHSAT102891 promoter region were amplified and different SNP sites (rs6230 and rs3792747) were selected as described above using the following primers sequences: upstream: *5'-GCTAGCAGCCAAGGAAAGGAAAGCTC-3'* (for-ward), downstream: *5'-TAAGCAGCAGGATTAG-*

GACTCGAG-3' (reve-rse). The target fragments were inserted into the PmirGLO-Vector (Promega) to construct the recombinant plasmids designated pmirGLO-AT and pmirGLO-GC, respectively, and sent to Chengdu Qingke Company for plasmid DNA synthesis. The recombinant plasmids were transfected into HEK-293T cells and the difference in the amount of luciferase protein expressed by the A-T and G-C haplotypes consisting of rs6230 and rs3792747 was detected.

Cell lines and cell culture

HEK-293T cell lines, provided by the National collection of authenticated cell cultures, were used for recombinant vector transfection and assessed by routine PCR and microscopic analysis to ensure that no cells were contaminated with mycoplasma during the research process. HEK-293T cells were cultured at 37 ℃ under 5% CO_2 in Dulbecco's Modified Eagle's Medium (Gibco) containing 10% fetal bovine serum (Gibco), 1% GlutaMAX (Invitrogen, Carlsbad, CA, United States) and 1% sodium pyruvate (Invitrogen) were added.

Transfection and luciferase reporter gene assays

HEK-293T cells were seeded into 24-well plates (2×10^5 cells per well) and cultured for 24-36 h to 90% confluence before transfection in serum-free medium with equal amounts of plasmid-free enzyme-free water (as blank control group), pmirGLO-AT, pmirGLO-GC, and the empty PmirGLO-Vector (no promoter) using the LipofectamineTM 2000 kit (Invitrogen). pRL-TK Luciferase Control Reporter Vectors (Promega, Madison, WI, United States) were co-transfected into HEK-293T cells for 24-48 h as a normal control. Luciferase activity in equal numbers of cells from each group was then measured using the dual-luciferase reporter gene assay system (Promega, Madison, WI, United States) according to the manufacturer's instructions. After adding the LAR II reagent (Promega) and cell lysis solution, the optical signal was detected by BioTek PowerWave XS2 full-wavelength scanning spectrophotometer. the measurement reading was recorded as The fluorescence value F (Firefly luminescence) was measured and after adding the Stop and Glo ®Reagent, the fluorescence value R (Renilla luminescence) was measured. Relative luciferase activity was calculated as the ratio of fluorescence value F to fluorescence value R. All samples were analyzed in triplicate and experiments were repeated in three independent occasions.

Statistical analysis

Continuous variable data were expressed as mean ± SEM and the categorical variable data were expressed as numbers (percentages). Moreover, for comparison between groups, *t*-tests were used for continuous variables, and χ^2 tests were used for categorical variables. The genotype frequencies of rs6230 and rs3792747 were obtained by direct counting. The χ^2 test was used to analyze the distribution and Hardy-Weinberg equilibrium of rs6230 and rs3792747 genotypes in the two groups. The correlation between gene polymorphisms and disease was evaluated using odds ratio (OR) and 95% confidence interval (CI), with the OR values adjusted based on age and sex data. Codominant, dominant and recessive genetic models were used for comparative analysis.

In the haplotype correlation analysis, the luciferase activity corresponding to each configuration was expressed as the mean ± SD, and the differences among the experimental data were analyzed by one-way analysis of variance. $P < 0.05$ was considered to indicate statistical significance. All data were analyzed using SPSS 25.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

LncRNA NONHSAT102891 promoter genotypes and risk of depression

We first investigated the association of the rs6230 and rs3792747 variants of the lncRNA NONHSAT102891 promoter with the risk of depression. For this purpose, we summarized the frequency distribution of genotypes and alleles of lncRNA NONHSAT102891 SNP rs6230 and rs3792747 in depressed patients and controls. In the control group, the genotype frequencies of the two polymorphisms were both in Hardy–Weinberg equilibrium (rs6230 $P = 0.101$; rs3792747 $P = 0.104$). There were significant differences in genotype and allele frequencies between the case and control groups (Table 1).

After further stratification by degree of depressive episode, suicide attempt, first episode patient and family history, we observed a correlation between depressive episode stratification and depressive risk in the rs6230 polymorphism group. The frequency of the TC/CC genotype was 69.3% in patients with moderate depression, which was higher than that in patients with severe depression (60.3%) (TC/CC *vs* TT, 95%CI: 1.59 (1.08-2.35), $P = 0.019$). These findings indicated that the rs6230 TC/CC genotype is associated with an increased risk of moderate depression; however, there was no significant correlation between rs3792747 polymorphism and the four variables used for stratification ($P > 0.05$) (Table 2).

LncRNA NONHSAT102891 promoter haplotypes and the risk of depression

We also evaluated the association of the two SNP haplotypes (rs3792747 and rs6230) of the lncRNANONHSAT102891 promoter with the risk of depression. LD analysis showed that these two common polymorphisms had higher D' values and lower R2 values ($D' = 0.71$, $r^2 = 0.07$) in the control, indicating the existence of gene recombination between the two SNP and that both were suitable for haplotype reconstruction.

Haplotype reconstruction analysis based on the genotyping data of depressed patients and controls revealed that the CG haplotype was more common in the control group than in the depressed patients These findings indicated that the CG haplotype is significantly associated with reduced risk of depression [CG *vs* TA: 95%CI: 1.59 (0.21-0.83], $P = 0.01$. There was no significant correlation between other haploid types and risk of depression (Table 3).

Table 1 Genetic model genotype and allele frequencies of two long-chain non-coding RNA NONHSAT102891 promoter polymorphisms among depressed patients and controls and association with risk of depression, *n* (%)

Models	Polymorphisms	Control (*n* = 329)	Patients (*n* = 480)	Adjusted OR (95%CI)	*P* value
	rs6230				
Codominant	TT	109 (33.1)	170 (35.4)	1	
	TC	173 (52.6)	250 (52.1)	0.91 (0.66-1.24)	0.53
	CC	47 (14.3)	60 (12.5)	0.82 (0.52-1.30)	0.41
Dominant	TT	109 (33.1)	170 (35.4)	1	
	TC/TT	220 (66.9)	310 (64.6)	0.79 (0.57-1.10)	0.17
Recessive	TT/TC	282 (85.7)	420 (87.5)	1	
	CC	47 (14.3)	60 (12.5)	0.77 (0.49-1.23)	0.28
Allele	T	391 (59.4)	590 (61.5)	1	
	C	267 (40.6)	370 (38.5)	0.92 (0.75-1.12)	0.40
	rs3792747				
Codominant	TT	208 (63.2)	326 (67.9)	1	
	TC	113 (34.3)	137 (28.5)	0.77 (0.57-1.05)	0.17
	CC	8 (2.4)	17 (3.5)	1.36 (0.57-3.20)	0.48
Dominant	TT	208 (63.2)	326 (67.9)	1	
	TC/CC	121 (36.8)	154 (32.1)	0.84 (0.60-1.17)	0.31
Recessive	TT/TC	321 (97.6)	463 (96.5)	1	
	CC	8 (2.4)	17 (3.5)	1.47(0.63-3.45)	0.36
Allele	T	529 (80.4%)	789 (82.2)	1	0.65
	C	129 (19.6)	171 (17.8)	0.89 (0.69-1.15)	0.36

Odds ratio was adjusted by age and sex. OR: Odds ratio; CI: Confidence interval.

Effects of different haplotypes of lncRNA NONHSAT102891 promoters on transcriptional activity

Next, we tested the hypothesis that the G/C and A/T haplotypes change the transcriptional activity of the lncRNA NONHSAT102891 by comparing the luciferase reporter activity of HEK-293T cells transfected with the pmirGLO-AT and pmirGLO-GC constructs. There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group ($P > 0.05$) (Table 4), indicating that the G/C and A/T haplotypes do not alter the transcriptional activity of the lncRNA NONHSAT102891.

DISCUSSION

After excluding organic brain lesions, clinicians mainly identify depression on the basis of the key symptoms of the disease. However, the most important basis for diagnosis is still based on the patient's clinical manifestations, which are affected by the patient's subjective experience and the clinical experience of the doctor. Finding objective and effective molecular indicators for the diagnosis of depression is the current focus of clinicians. Depression-related biomarkers in the peripheral blood or brain are attracting increasing attention for the development and exploration of clinical objective diagnostic indicators. LncRNAs are known to play an important role in the normal functions of cells and the pathological consequences of disorders, which lays a molecular foundation for understanding the similarities and differences in the pathophysiological mechanisms behind depression. Using targeted reverse transcription PCR analysis of lncRNA expression levels in peripheral blood and brain tissue of depression patients or a mouse model of depression, Seki *et al* [23] found that the expression levels of Y5, MER11C, PCAT1, and PCAT29, were upregulated in patients with major depressive disorder compared to healthy controls, while the expression level of RMRP was downregulated. Low expression of RMRP in peripheral blood leukocytes of depressed patients and mice correlated strongly with the severity of the symptoms. Thus, these findings implicate RMRP in peripheral blood leukocytes as a potential biomarker of depression. Zhou *et al*[24] performed RNA-sequencing in the rostral anterior cingulate cortex of 26 depressed suicidal individuals and 24 controls who died naturally or by accident with no history of psychopathology, and identified 23 differentially expressed lncRNAs, including SNORD3C and ZNF833P, and their differentially expressed overlapping and

Table 2 Stratified analyses of the rs6230 and rs3792747 polymorphisms in depressed patients

Variables	Frequency (%)		Adjusted OR (95%CI)	*P* value
rs6230				
Depressive episode	Severe	Mild		
TT	100 (39.7)	70 (30.7)	1.00 (Ref)	
TC	125 (49.6)	125 (54.8)	1.57 (1.05-2.36)	0.28
CC	27 (10.7)	33 (14.5)	1.69 (0.92-3.09)	0.088
TC/CC	152 (60.3)	158 (69.3)	1.59 (1.08-2.35)	0.019
Suicide attempt	Yes	No		
TT	102 (34.9)	68 (36.2)	1.00 (Ref)	
TC	154 (52.7)	96 (51.1)	1.06 (0.70-1.63)	0.78
CC	36 (12.3)	24 (12.8)	0.87 (0.45-1.68)	0.68
TC/CC	190 (65.1)	120 (63.8)	1.02 (0.68-1.54)	0.91
First-episode patient	Yes	No		
TT	88 (35.5)	82 (35.3)	1.00 (Ref)	
TC	131 (52.8)	119 (51.3)	1.07 (0.71-1.60)	0.75
CC	29 (11.7)	31 (13.4)	1.15 (0.63-2.10)	0.66
TC/CC	160 (64.5)	150 (64.7)	1.08 (0.73-1.58)	0.70
Family history	Yes	No		
TT	37 (39.4)	133 (34.5)	1.00 (Ref)	
TC	47 (50)	203 (52.6)	1.29 (0.79-2.11)	0.31
CC	10 (10.6)	50 (12.9)	1.44 (0.66-3.14)	0.35
TC/CC	57 (60.6)	253 (65.5)	1.30 (0.81-2.07)	0.28
rs3792747				
Depressive episode	Severe	Mild		
TT	176 (69.8)	150 (65.8)	1.00 (Ref)	
TC/CC	76 (30.2)	78 (34.2)	1.21 (0.82-1.80)	0.33
Suicide attempt	Yes	No		
TT	201 (68.8)	125 (66.5)	1.00 (Ref)	
TC/CC	91 (31.2)	63 (33.5)	1.14 (0.75-1.72)	0.54
First-episode patient	Yes	No		
TT	168 (67.7)	158 (68.1)	1.00 (Ref)	
TC/CC	80 (32.3)	74 (31.9)	0.98 (0.66-1.44)	0.9
Family history	Yes	No		
TT	64 (68.1)	262 (67.9)	1.00 (Ref)	
TC/CC	30 (31.9)	124 (32.1)	1.00 (0.62-1.63)	1.00

Odds ratio was adjusted by age and gender. OR: Odds ratio; CI: Confidence interval.

antisense protein-coding genes, several of which were associated with interferon signaling. Bioinformatics approaches have also been adopted to identify differential expression of depression-related genes. Liu *et al*[25] analyzed the genes for seven mental traits identified in large-scale GWAS and found that LINC00461 has a pleiotropic effect and is associated with five mental traits, including depression, schizophrenia, and Alzheimer's disease. Als *et al*[26], identified 243 risk loci in more than 1.3 million individuals through GWAS and found that depression is highly polygenic, which could help deepen depression research and precise treatment. This information provides a better understanding of the genetic associations of depression and could aid in the development of more effective treatments.

Table 3 Haplotype analysis of rs3792747 and rs6230 in depressed patients and controls, *n* (%)

Haplotype	Depressed patients	Controls	OR (95%CI)	*P* value
T/A	433 (45.1)	284 (43.2)	1.00	
T/G	356 (37.1)	245 (37.2)	0.95 (0.76-1.19)	0.67
C/A	157 (16.4)	107 (16.3)	0.96 (0.72-1.28)	0.79
C/G	14 (1.5)	22 (3.3)	0.42 (0.21-0.83)	0.01

OR: Odds ratio; CI: Confidence interval.

Table 4 Relative luciferase activity of control and case groups

Group	RFA	OR (95%CI)	*P* value
Control	1.58 ± 0.28	1.00	
EV	1.52 ± 0.22	0.080 (-0.526-0.542)	0.973
p-G/C	1.59 ± 0.27	-0.006 (-0.540-0.528)	0.979
p-A/T	1.57 ± 0.29	0.060 (-0.474-0.594)	0.802

Data represent the mean ± SEM. RFA value: The ratio of luciferase activity of recombinant plasmid to that of Renilla. EV: Empty vector; OR: Odds ratio; CI: Confidence interval.

In this study, we explored the possible association of other SNPs and haplotypes in the lncRNANONHSAT102891 promoter region with susceptibility to depression in a Chinese population. Our results suggest that the TC/CC genotype of rs6230 in the lncRNA NONHSAT102891 promoter region may be associated with the risk of moderate depression. In the haplotype analysis of rs3792747 and rs6230, the frequency of the CG haplotype was more common in the patients with severe depression than in the control group, indicating that the haplotype was associated with a reduced risk of depression. However, no significant correlation was found between the two haplotypes and lncRNA NONHSAT102891 promoter transcriptional activity in dual-luciferase reporter assays.

In recent years, lncRNAs have provided significant advances in our understanding of the pathogenesis of severe depression as well as its diagnosis and treatment. Li *et al*[22] suggested that nine lncRNA, including NONHSAT102891, TCONS_00019174, and ENST00000566208, may be biomarkers of MDD. LncRNAs can participate in the epigenetic, transcriptional, and post-transcriptional regulation of the pathogenesis of depression. LncRNA XR351665 has been reported to promote the development of chronic pain-induced depression by upregulating DNMT1 *via* sponge miR-152-3p[27]. Long-intergenic non-coding RNA (Linc) 01360 expression is affected by rs70959274Alu polymorphism, and the Alu insertion induces DNA methylation, which significantly reduces the transcriptional activity of linc01360 compared with the control group, thus reducing the genetic risk of human MDD[14]. Differentially expressed lncRNAs also affect the pathogenesis of depression by participating in the regulation of a variety of signaling pathways. Microdeletion of FAAH-OUT lncRNA expressed in the brain and dorsal root ganglia led to downregulation of FAAH expression and a sharp increase in BDNF levels, thereby reducing the risk of depression and anxiety[28]. Decreased levels of lncRNAMIR155HG were shown to induce increased microRNA (miR)-155 expression in the hippocampus and inhibit BDNF expression, leading to depression-like behavior in a chronic unpredictable mild stress model of depression in mice. MiR-155HG/miR-155/BDND axis damage is a key cause of depression[29]. Low levels of linc00473 and upregulated expression of FEDORA in prefrontal cortex (PFC) neurons were detected in female depressed patients; the expression of linc00473 affected the pre-and postsynaptic features of mPFC pyramidal neurons and participated in regulation of the cAMP response element binding protein (CREB), and low levels of linc00473 in PFC neurons promoted stress recovery in female mice[30-32]. Selective expression of FEDORA in mouse mPFC neurons or oligodendrocytes confirmed its role as a sex-specific regulator of anxiety and depression-like behavior, since this phenomenon occurred only in female mice. Abedpoor *et al*[33] found that exercise and leucine consumption can alleviate depression-related behaviors by increasing the expression of four lncRNAs (MEG3, HOTAIR, GAS5 and TUG1 related to KDR/VEGF-α/PTEN/BDNF) in the lncRNA network of the brain-gut axis in depression-like mice. KEGG enrichment analysis revealed the involvement of important signaling pathways such as hippo, MAPK, Wnt, PI3K/Akt, cGMP-PKG, RAS, and IL-17 in the regulation of hippocampal function or pathological processes associated with depression[34-38]. For example, overexpression of lncRNA TCONS_00019174 can activate the Wnt classical pathway in mice, inactivating GSK3β phosphorylation, while also upregulating β-catenin protein expression, thereby exerting antidepressant effects in mice[39]. Silencing lncRNA GAS5 can activate the PI3K/AKT pathway to protect hippocampal neurons from depression-like injury by regulating the miR-26a/EGR1 axis[40]. LncRNA84277 ameliorated chronic pain-associated depressive-like behavior by upregulating SIRT1 expression *via* the competitive sponge miR-128-3p[41]. Thus, there is accumulating evidence that these biomarkers play a key role in the pathogenesis of depression and provide new targets for the treatment of depression.

The limitations of current research should be noted. First, the case group comprised 71% females and only 29% males. The incidence of depression is sex-biased, and the higher heritability of women than men may lead to a higher incidence of depression in women[42]. Therefore, the role of epigenetic factors in the occurrence and development of depression represents an important focus of future research. Evaluating the effect of lncRNA on depression and targeted control of the phenotype of depression in a research population will promote the discovery of new and more effective treatments. Second, due to the limited sample size, the results of this study may be biased, and further studies with a larger sample size are required to determine the reference expression range of biomarkers. Third, existing evidence suggests that patients with late-onset depression have more severe and frequent patchy lesions in the deep frontal white matter and basal ganglia detected by magnetic resonance imaging as compared with the control groups or patients with early-onset depression[43]. Due to barriers such as the lack of scientific basis for diagnostic systems and structures, uncertainty in brain function, indeterminate time-course of recovery in patients with functional mental disorders, and lack of diagnostic tools, no causal relationships have been identified for functional mental disorders such as depression[44]. In the future, we aim to explore a multidimensional framework that incorporates epigenetic and neurological impact data, thereby enhancing the practical ability of clinicians to diagnose[45].

CONCLUSION

Our results indicate that the rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter are related to a reduced risk of depression in the Han Chinese population.

ARTICLE HIGHLIGHTS

Research background

Depression is a common life-threatening and disabling mental illness, and long-chain non-coding RNA (lncRNA) abnormal expression may affect the pathophysiological processes of depression. Our previous study reported that the single-nucleotide polymorphism (SNP) rs155979 GC in the promoter region of lncRNA NONHSAT102891 affects depression susceptibility in a Chinese population.

Research motivation

The complex interplay of species between major depressive disorder and lncRNA remains unclear.

Research objectives

To explored associations between two SNPs and haplotypes within lncRNA NONHSAT102891 promoter region and depression susceptibility in Chinese population.

Research methods

We conducted a case-control study in a cohort of 480 patients with depression and 329 healthy controls, and performed genotyping by gene sequencing. The function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes was detected by dual-luciferase reporter assays of human embryonic kidney 293T transfected cells.

Research results

The degree of mild depressive episodes associated with the rs6230 TC/CC genotype increased by 1.59 times. The haploid analysis revealed linkage disequilibrium between rs3792747 and rs6230, and the double SNP CG haplotype was more common in the control group compared to case group, indicating that this haplotype significantly reduced the risk of depression (C/G *vs* T/A: odds ratio = 0.42, 95% confidence interval: 0.21-0.83, P = 0.01). There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P > 0.05).

Research conclusions

The rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter may be associated with a reduced risk of depression in the Chinese population. However, further studies with a larger sample size are required to determine the reference expression range of biomarkers.

Research perspectives

This study provides insights into the early prediction and diagnosis of depression and important clues for development of tools that will facilitate more accurate diagnosis and treatment of depression in the clinic.

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FOOTNOTES

Author contributions: Liang YD designed the study and corrected the manuscript; Li Y performed the majority of experiments and wrote the manuscript; Wang YX, Tang XM, Liang P, Chen JJ, Jiang F, Yang Q participated to the data collection and analysis of human material, and commented on previous versions of the manuscript; all authors contributed to the study conception and design. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and risk factors for anxiety and depression after mini-incision hip arthroplasty for femoral head osteonecrosis

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Abstract

BACKGROUND

Osteonecrosis of the femoral head (ONFH) is a prevalent orthopedic issue, leading to the collapse and fragmentation of the femoral head in its advanced stages, which can severely impair patients' quality of life. Total hip arthroplasty (THA) is a clinical intervention frequently used to alleviate ONFH symptoms and reinstate hip functionality. The conventional surgical technique is invasive and comes with an extended recuperation period, posing significant challenges for patients. With the progression of medical technology, the use of the mini-incision technique in minimally invasive THA (MITHA) has become more prevalent. However, comparative studies examining the effectiveness of these two surgical procedures in treating ONFH remain scarce. Furthermore, understanding patients' psychological well-being is crucial given its profound influence on postoperative recuperation.

AIM

To evaluate the impact of mini-incision MITHA on ONFH treatment and to identify the risk factors associated with postoperative anxiety and depression.

METHODS

A retrospective study was conducted on 125 patients treated for ONFH at Xi'an Hong Hui Hospital between February 2020 and January 2022, with the term "consecutive" indicating that these patients were treated in an unbroken sequence without any selection. Among these, 60 patients (control group) underwent traditional THA, while 65 patients (observation group) were treated with mini-incision MITHA. Variations in the visual analog scale (VAS) score and the Harris hip score were monitored. Additionally, shifts in pre- and posttreatment Hamilton anxiety (HAMA) and Hamilton depression (HAMD) scale scores were recorded. Patients with both postoperative HAMA and HAMD scores of ≥ 8 were

identified as those experiencing negative emotions. Logistic regression was utilized to analyze the determinants influencing these negative emotional outcomes. Comparative analyses of surgical and postoperative metrics between the two groups were also conducted.

RESULTS

Posttreatment results indicated a significantly higher VAS score in the control group than in the observation group, while the Harris score was considerably lower ($P < 0.0001$). The observation group benefited from a notably shorter operation duration, reduced blood loss, diminished incision size, and a decreased postoperative drainage time ($P < 0.0001$), accompanied by a reduced hospital stay and lower treatment costs ($P < 0.0001$). The control group had elevated posttreatment HAMA and HAMD scores in comparison to the observation group ($P < 0.0001$). Multivariate logistic regression revealed that being female [odds ratio (OR): 4.394, 95%CI: 1.689-11.433, $P = 0.002$], having a higher postoperative VAS score (OR: 5.533, 95%CI: 2.210-13.848, $P < 0.0001$), and having higher treatment costs (OR: 7.306, 95%CI: 2.801-19.057, $P < 0.0001$) were significant independent determinants influencing postoperative mood disturbances.

CONCLUSION

Compared to conventional THA, mini-incision MITHA offers advantages such as reduced operation time, minimal bleeding, and a shorter incision in ONFH patients. Moreover, factors such as sex, postoperative pain (reflected in the VAS score), and treatment costs significantly impact postoperative anxiety and depression.

Key Words: Necrosis of the femoral head; Total hip arthroplasty; Minimally invasive total hip arthroplasty; Postoperative recovery; Anxiety; Depression

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Core Tip: Minimally invasive total hip arthroplasty has shown significant advantages in the treatment of osteonecrosis of the femoral head, including a short operation time and less bleeding. However, the psychological stress of postoperative patients, especially female patients, those with high postoperative pain scores, and those with high treatment costs, cannot be ignored as these patients are more susceptible to adverse emotions. Therefore, although improvements in technology and surgical methods are essential, psychological counseling, which can help improve the treatment effect and the quality of life of patients, is equally important.

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INTRODUCTION

Necrosis of the femoral head (ONFH) is a disease that causes partial or total ischemia of the femoral head due to blood circulation interruption or injury, which leads to the death of osteocytes, bone marrow hematopoietic cells and adipocytes and may eventually trigger a series of structural changes, such as femoral head collapse[1]. Such a disease is considered to be a disease with a high disability rate in orthopedics[2]. Early diagnosis of ONFH is challenging due to the atypicality of its clinical presentation[3]. As the condition worsens, the femoral head collapses on images, and complete loss of the original femoral head shape occurs in severe cases, which can further develop into degenerative hip osteoarthritis[4]. Therefore, choosing effective treatment methods to improve the patient's condition is critical.

Clinically, total hip arthroplasty (THA) is a common treatment that can achieve joint function reconstruction in patients with ONFH, thus significantly improving patient quality of life[5]. However, conventional THA has some drawbacks, such as a large incision, heavy trauma, and a high incidence of surgical complications[6,7]. Hence, it is necessary to reduce the risk of surgical trauma and complications while ensuring the safety and effectiveness of surgery. In recent years, there has been an increase in the application of minimally invasive THA (MITHA) with the development of minimally invasive technology[8]. This procedure has the advantages of less trauma and quick recovery, which can more effectively help patients relieve pain and restore joint function[9,10]. However, whether MITHA is advantageous over conventional THA with a more significant effect on improving patients' conditions remains to be further studied.

Currently, the treatment of ONFH relies mainly on surgery, which results in a long recovery time, especially for elderly patients. During the recovery period, patients may experience a great reduction or even loss of self-care ability, as well as varying degrees of motor system damage. These factors have placed great pressure on the physiology and psychology of patients, predisposing them to psychological stress and negative emotions (NEs).

Accordingly, the purpose of this study was to explore the effect of MITHA in the treatment of ONFH and to analyze the risk factors that may affect postoperative anxiety and depression. This study can provide more rigorous evidence for clinical treatment and intervention, with important practical significance for improving patient quality of life and mental health.

MATERIALS AND METHODS

Patient data

A retrospective analysis was performed on 125 ONFH patients who were treated at Xi'an Hong Hui Hospital from February 2020 to January 2022. Among them, 60 patients who received conventional THA and 65 patients who received MITHA were assigned to the control group and observation group, respectively.

Eligibility and exclusion criteria

The inclusion criteria were as follows: (1) Patients whose physical condition was at an acceptable level and with an American Association of Anesthesiologists score ranging from 1 to 3 points[11]; (2) Those meeting the indications for THA; (3) Diagnosis of CNFH by imaging examination; (4) Awareness of and voluntary participation in the study by patients and their families; (5) Unilateral lesions that met surgical indications; and (6) Complete clinical data.

The exclusion criteria were as follows: (1) Severe cardio-cerebrovascular diseases and other chronic wasting diseases; (2) Multiple hip replacement procedures; (3) Concurrent surgery of other parts; (4) Incomplete information or loss to follow-up; or (5) Active infection in the affected hip or surgical area.

Treatment methods

Patients in the control group underwent conventional THA. The procedure was performed under general anesthesia with the patient placed in a lateral decubitus position. After successful anesthesia, the surgeon successively cut the skin of the patient to expose the femoral head and the acetabulum edge, viewing the acetabulum damage and repairing it. Then, an appropriate prosthesis was selected for implantation according to the patient's specific condition. After confirmation of the correct placement of the implant, the surgeon cleaned the incision and placed a drainage tube to complete the procedure.

Patients in the observation group underwent MITHA using a mini-incision technique, with the anesthesia method and surgical position the same as the control group. During the operation, the surgeon made a small incision of 6 to 10 cm along the gluteus maximus muscle fibers on the posterior side of the greater trochanter of the femur. The gluteus maximus muscle was then cut open, and the external rotators at the attachment of the trochanter were cut off and pulled posteriorly so that the joint capsule could be exposed for incision to expose the femoral head and acetabulum. Then, within 10 to 15 cm of the femur, the surgeon used a chainsaw to cut the neck of the femur and remove the severed femoral head. Next, the stump of the ligamentum teres of the acetabulum and the glenoid lip were removed, and the exposed ligamentum teres fossa was ground flat. At the same time, reaming was performed on the acetabulum with an anteversion angle of 20° and an abduction angle of 45°. Then, a prosthesis with a suitable size was selected for a trial mold, and the prosthesis was implanted after confirming its stability and tightness. At the end of the surgery, the surgeon drilled 3 to 4 holes in the suture of the external rotators, washed the operation field and placed a drainage tube to end the operation. Both groups received routine anti-infection therapy after surgery.

Clinical data collection

The following information was collected: (1) Clinical data, namely, age, sex, body mass index (BMI), pathogeny, affected side, smoking history, alcoholism history, education level, annual income and marital status; (2) Surgical indicators, namely, operation time, intraoperative blood loss, incision length, and postoperative drainage time; (3) Postoperative indicators, namely, length of stay and treatment cost; (4) Scoring indices, namely, visual analog scale (VAS) scores[11] and Harris hip score (HHS) before and after operation; and (5) Pre- and posttreatment Hamilton anxiety and depression scale scores, namely, the Hamilton anxiety scale (HAMA) and Hamilton depression scale (HAMD) scores[12].

Outcome measures

Primary outcome measures: Changes in VAS and HHS scores before and after treatment were observed. Alterations in pre- and posttreatment HAMA and HAMD scores were compared between the two groups. According to postoperative scores, patients with both HAMA and HAMD scores ≥ 8 were considered to have NEs, and the risk factors affecting the occurrence of NEs were analyzed by logistic regression.

Secondary outcome measures: Clinical data, surgical indicators and postoperative indicators were compared.

Statistical analysis

SPSS 26.0 and GraphPad Prism 9 were used for data analysis, and the threshold of statistical significance was $P < 0.05$. Count data are expressed as frequencies (percentages), and comparisons between groups were made by means of the χ^2 test. Measurement data are expressed as the mean ± SD. Two independent samples t tests were used for comparisons between groups, independent samples t tests were used for comparisons between groups, and paired t tests were used for comparisons within groups. Logistic regression was used to analyze the risk factors affecting patients' NEs.

RESULTS

Comparison of clinical data

In the comparisons of the patients' clinical data, it was found that the observation and control groups were not significantly different in age, sex, BMI, pathogeny, affected side, smoking history, alcoholism history, education level, annual income, or marital status ($P > 0.05$, Table 1).

Changes in pain and functional scores

Changes in VAS and HHS scores before and after treatment were compared between groups. The two groups did not differ significantly in terms of their pretreatment VAS or HHS scores ($P > 0.05$). A reduction in the VAS score and an increase in the HHS score were observed in both groups after treatment ($P < 0.0001$). Further intergroup comparison revealed a higher VAS score and a lower HHS score in the control group than in the observation group ($P < 0.0001$, Figure 1).

Comparison of surgical indices

The intergroup comparison of surgical indices showed that the operation time was significantly shorter in the observation group than in the control group, with less intraoperative blood loss, shorter incision length, and less postoperative drainage time ($P < 0.0001$, Figure 2).

Comparison of postoperative indices

Comparing the postoperative indices, it was found that the length of stay and treatment cost of patients were significantly lower in the observation group than in the control group ($P < 0.0001$, Figure 3).

Evaluation of patients' NEs

Patients' anxiety and depression were evaluated before and after treatment. There were no significant difference in the pretreatment HAMA or HAMD scores between the two groups ($P > 0.05$). However, significantly reduced HAMA and HAMD scores were observed in both groups after treatment ($P < 0.0001$). Further comparison showed that the posttreatment HAMA and HAMD scores were significantly higher in the control group than in the observation group ($P < 0.0001$, Figure 4).

Analysis of risk factors affecting patients' NEs

We conducted a statistical evaluation of the postoperative HAMA and HAMD scores. Using a screening threshold of a postoperative score ≥ 8, we identified 71 patients exhibiting postoperative anxiety and 77 manifesting postoperative depression. Based on these findings, patients were categorized into two distinct groups: the NE group ($n = 71$) and the emotional stability group ($n = 54$). In the univariate analysis, several factors emerged as potential risk determinants affecting patients' NEs. These included age ≥ 60 years, female sex, an education level below middle school, an annual income less than 50000 CNY, opting for the conventional surgical plan, elevated postoperative VAS scores, prolonged operation times, and increased treatment costs ($P < 0.05$, Table 2). To refine our understanding, we assigned numerical values to the identified variables, as shown in Table 3. Our subsequent multivariate logistic regression analysis highlighted three prominent factors. Specifically, being female, having a higher postoperative VAS score, and incurring elevated treatment costs were significant independent risk factors influencing postoperative NEs in patients ($P < 0.01$, Table 4).

DISCUSSION

ONFH is a common condition in orthopedics with symptoms such as femoral head collapse and fragmentation in the later stage, which can cause great pain to patients and even loss of mobility[13]. The interruption of the blood supply to the femoral head leads to the production of free radicals, as well as hypoxia and reperfusion injury, which can accelerate osteocyte death and eventually lead to the necrosis of bone marrow stromal stem cells or the formation of adipocytes, leading to local osteoporosis[14]. Hip replacement has been clinically shown to be an effective method to relieve hip pain and restore hip function in ONFH patients[15]. However, this procedure is highly invasive and is associated with a long postoperative recovery period and long-term bed rest, which increases the difficulty of rehabilitation training and the risk of developing lower extremity deep venous thrombosis, affecting postoperative rehabilitation.

The development of minimally invasive surgery technology has enabled the gradual application and popularization of mini-incision MITHA in clinical practice[16]. In addition, the rapid development of medical technology and equipment has made it possible to improve and optimize the incision method of THA[17]. In long-term clinical practice, mini-incision THA has become a standard surgical approach with many advantages. However, little has been reported about the difference between conventional and minimally invasive THA procedures for the treatment of ONFH. Repantis *et al* [18] found no significant difference in intraoperative blood loss between the two THA methods but identified markedly lower postoperative pain scores in the minimally invasive group. The present study also comparatively analyzed the two surgical modalities and found a significantly shorter operation time in patients undergoing MITHA *vs* those receiving conventional THA, with less intraoperative bleeding, a shorter incision length, less surface peeling and clear joint exposure, which greatly shortened the operation time and reduced the body's traumatic stress response.

Table 1 Comparison of clinical data

Factors		Control group (*n* = 60)	Observation group (*n* = 65)	*P* value
Age				0.569
	≥ 60 years old	34	40	
	< 60 years old	26	25	
Sex				0.650
	Male	34	40	
	Female	26	25	
BMI				0.503
	≥ 25 kg/m^2	15	13	
	< 25 kg/m^2	45	52	
Pathogeny				0.434
	Trauma	29	22	
	Hormone	20	27	
	Alcohol	7	10	
	Others	4	6	
Affected side				0.264
	Left	27	36	
	Right	33	29	
Smoking history				0.650
	With	34	40	
	Without	26	25	
History of alcoholism				0.444
	With	5	8	
	Without	55	57	
Education level				0.490
	≥ Junior high school	25	23	
	< Junior high school	35	42	
Annual income				0.531
	≥ 50000 CNY	18	16	
	< 50000 CNY	42	49	
Marital status				0.569
	Married	44	50	
	Divorced	9	10	
	Others	7	5	

BMI: Body mass index.

For patients with either osteoporotic fracture or ONFH, THA will cause psychological stress and cause greater psychological pressure[19]. Anxiety and depression are the most common psychological complications, both of which have a certain impact on patients' cognitive and psychological states[19,20]. In addition, anxiety and depression can significantly reduce patients' motivation and adherence to treatment during hospitalization, leading to a significant decline in treatment effectiveness. Evidence has shown that psychological factors have an impact on the outcome of THA[21]. In contrast, a good state of mind helps patients recover as quickly as possible. Therefore, identifying factors that influence anxiety and depression helps clinical medical staff to take relevant nursing measures and carry out targeted treatment in time. In our study, anxiety and depression were found before surgery in both groups and were relieved in some patients after treatment. To determine the risk factors for postoperative NEs in ONFH patients, we performed a regression

Table 2 Univariate analysis

Factors		Negative emotion group (*n* = 71)	Emotional stability group (*n* = 54)	*P* value
Age				0.002[b]
	≥ 60 years old	50	24	
	< 60 years old	21	30	
Sex				0.003[b]
	Male	34	40	
	Female	37	14	
BMI				0.460
	≥ 25kg/m^2	14	14	
	< 25kg/m^2	57	40	
Pathogeny				0.423
	Trauma	33	18	
	Hormone	25	22	
	Alcohol	9	8	
	Others	4	6	
Affected side				0.937
	Left	36	27	
	Right	35	27	
Smoking history				0.060
	With	37	37	
	Without	34	17	
History of alcoholism				0.866
	With	7	6	
	Without	64	48	
Education level				0.026[a]
	≥ Junior high school	21	27	
	< Junior high school	50	27	
Annual income				0.038[a]
	≥ 50000 CNY	14	20	
	< 50000 CNY	57	34	
Marital status				0.752
	Married	52	42	
	Divorced	11	8	
	Others	8	4	
Treatment methods				0.032
	Minimally invasive	31	34	
	Conventional	40	20	
Postoperative VAS score		4.28 ± 1.59	2.70 ± 1.50	< 0.0001[d]
Postoperative harris hip score		79.50 ± 8.06	80.33 ± 8.77	0.585
Operation time (min)		95.69 ± 8.36	92.63 ± 7.18	0.033[a]
Intraoperative blood loss (mL)		14.15 ± 3.89	11.57 ± 4.23	0.074
Incision length (cm)		436.59 ± 190.14	441.17 ± 210.32	0.898

Postoperative drainage time (min)	459.11 ± 203.95	343.56 ± 192.78	0.075
Length of stay (d)	11.26 ± 2.96	12.29 ± 4.16	0.109
Treatment cost (CNY)	40006.21 ± 5472.16	34272.05 ± 6033.42	< 0.0001[d]

[a]$P < 0.05$.
[b]$P < 0.01$.
[d]$P < 0.0001$.
BMI: Body mass index; VAS: Visual analogue scales.

Table 3 Assignment table

Factors	Assignment
Age	≥ 60 years old = 1, < 60 years old = 0
Sex	Male = 0, female = 1
Education level	≥ Junior high school = 0, < Junior high school = 1
Annual income	≥ 50000 CNY = 0, < 50000 CNY = 1
Surgical plan	Minimally invasive = 0, conventional = 1
Postoperative VAS score	≥ 4 = 1, < 4 = 0
Operation time	≥ 95 min = 1, < 95 min = 0
Treatment cost	≥ 35000 CNY = 1, < 35000 CNY = 0
Anxiety and depression	Negative emotion group = 1, emotional stability group = 0

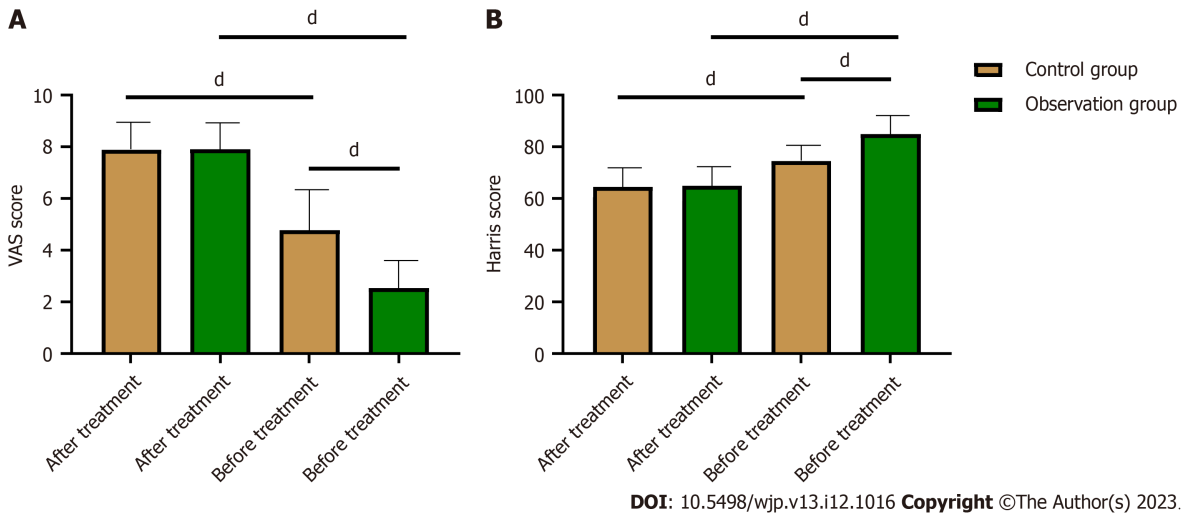
VAS: Visual analogue scales.

Table 4 Multivariate analysis

Factors	β	Standard error	χ^2	*P* value	OR	95%CI	
						Lower bound	Upper bound
Age	0.578	0.465	1.545	0.214	1.782	0.716	4.434
Sex	1.480	0.488	9.206	0.002[b]	4.394	1.689	11.433
Education level	0.809	0.462	3.064	0.080	2.246	0.908	5.557
Annual income	0.704	0.521	1.829	0.176	2.023	0.729	5.614
Surgical plan	0.183	0.487	0.141	0.707	1.201	0.462	3.120
Postoperative VAS score	1.711	0.468	13.354	<0.001[c]	5.533	2.210	13.848
Operation time	0.643	0.494	1.695	0.193	1.902	0.723	5.004
Treatment cost	1.989	0.489	16.532	<0.001[c]	7.306	2.801	19.057

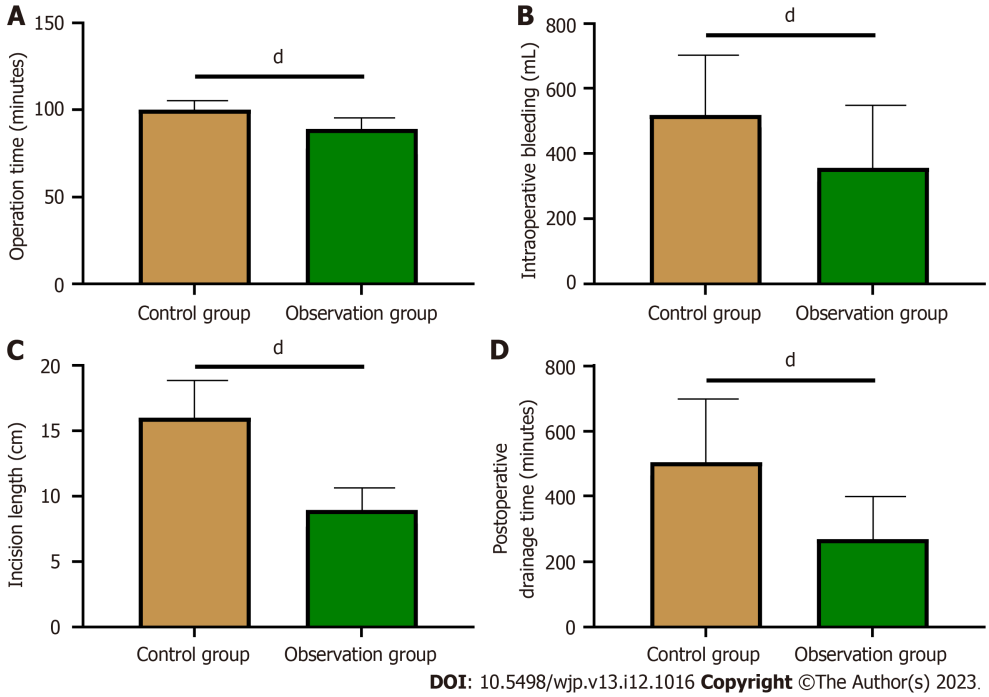
[b]$P < 0.01$.
[c]$P < 0.001$.
VAS: Visual analog scales; OR: Odds ratio.

analysis. The results showed that sex, postoperative VAS score, and treatment cost were risk factors for postoperative NEs in ONFH patients. The reason may be that women, who are affected by psychological and physiological characteristics, are more sensitive and emotional and therefore more susceptible to NEs after illness. In addition, the activity limitation of postsurgical patients leads to aggravated depression and anxiety. In the research of Liu and Wang[22], the incidence of anxiety and depression increased significantly among female patients after gastric cancer surgery and was related to poor prognosis, which was the main risk factor. Pain itself is a kind of physical discomfort that can negatively affect the individual's mood and behavior. Pain can also lead to decreased sleep quality, further aggravating the patient's emotional distress. Persistent pain can cause the patient to worry about the prospect of future recovery, exacerbating anxiety and depression. Park *et al*[23] suggested that severe postoperative pain was a risk factor for postoperative anxiety and depression in patients with lung cancer. Although ONFH does not require long-term treatment, conventional



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Figure 1 Changes of visual analogue scales and Harris hip score scores in patients before and after treatment. A: Comparison of visual analogue scales score; B: Comparison of Harris hip score; VAS: Visual analogue scales. $^{d}P < 0.0001$.

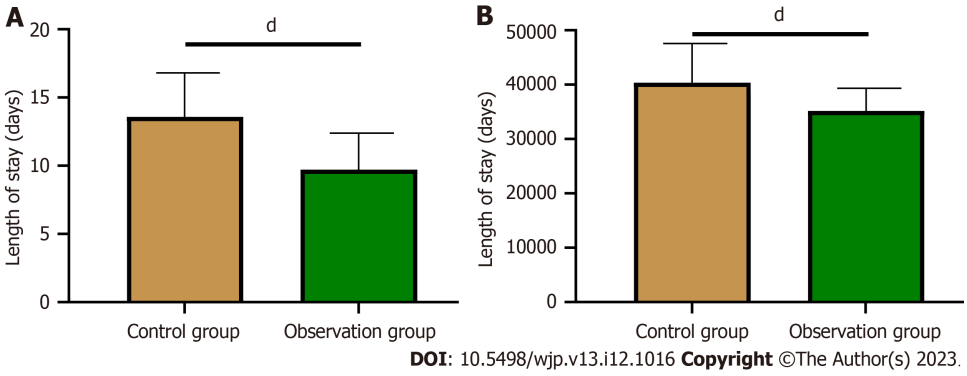


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Figure 2 Comparison of surgical indexes. A: Comparison of operation time; B: Comparison of intraoperative blood loss; C: Comparison of incision length; D: Comparison of postoperative drainage time. $^{d}P<0.0001$.

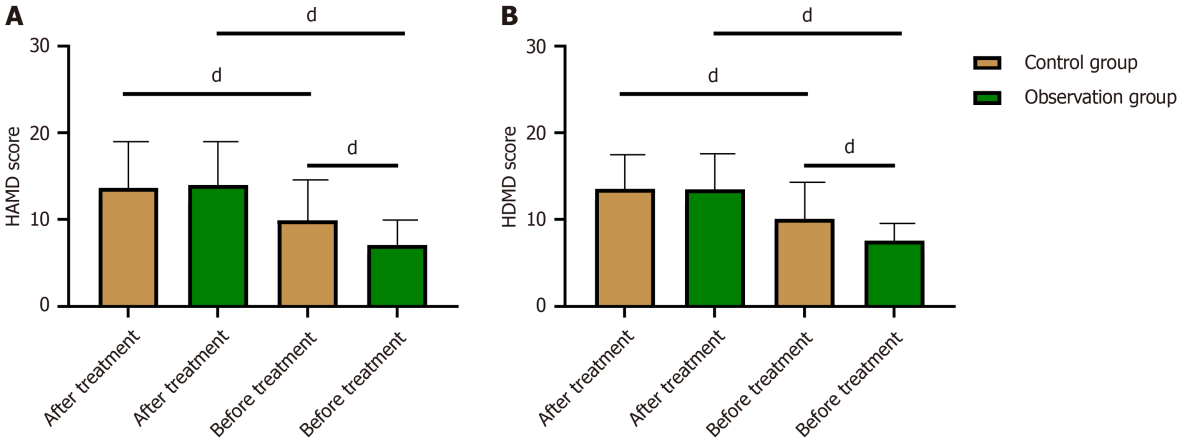
replacement surgery is not affordable for all families, increasing the financial burden on patients' families. In addition, from the perspective of the patients, the psychological pressure felt is enormous due to fear of becoming a burden to their families. They may also worry that they will not be able to pay for medical expenses in the long term and that follow-up treatment will be difficult to guarantee, resulting in negative feelings such as guilt and anxiety[24,25]. Therefore, to improve patients' psychological states, it is necessary to strengthen communication with patients and encourage them to express their inner thoughts. For patients with NEs, targeted psychological counseling can be implemented to help relieve stress. In addition, those patients with effectively controlled conditions after treatment and a good state of mind can be invited to share their treatment experiences and exchange opinions on overcoming difficulties. Such measures are helpful to improve patients' confidence in treatment and prevent the occurrence of NEs.

In this study, we determined the therapeutic effect of MITHA on ONFH patients and the risk factors for postoperative NEs through analyses. However, this study still has some limitations. First, the insufficient sample size may lead to errors in the results of the regression analysis. Second, patients' long-term follow-up cannot be determined due to the retrospective nature of this study, resulting in uncertainty regarding the long-term outcomes of patients treated by the two surgical methods. Finally, as a single-center study, the applicability and generalizability of the results of this study need



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Figure 3 Comparison of postoperative indexes. A: Comparison of length of stay; B: Comparison of treatment cost. $^{d}P<0.0001$.



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Figure 4 Changes of Hamilton anxiety scale and Hamilton depression scale scores before and after treatment. A: Comparison of Hamilton anxiety scale score; B: Comparison of Hamilton depression scale score. HAMA: Hamilton anxiety scale; HAMD: Hamilton depression scale. $^{d}P<0.0001$.

to be validated and supported by external data. Therefore, the hope is that more in-depth research can be carried out in the future and that more samples will be collected to support the conclusions of this study.

CONCLUSION

In this paper, the application and clinical effectiveness of THA in ONFH patients, particularly the influence of MITHA on patients' treatment outcomes, were studied. The results show that MITHA contributes to a shorter operation time, less blood loss and a shorter incision length. At the same time, anxiety and depression before surgery were prevalent in all patients, and these NEs may be related to the patient's sex, postoperative pain score, and treatment cost.

ARTICLE HIGHLIGHTS

Research background

Osteonecrosis of the femoral head (ONFH) is a complex and multifactorial disease, which can seriously affect the quality of life of patients at the advanced stage. Although conventional total hip arthroplasty (THA) is effective in relieving symptoms, the procedure is invasive, resulting in a long recovery period for patients. Minimally invasive THA (MITHA) has begun to be used clinically with the development of minimally invasive techniques.

Research motivation

There is a lack of studies comparing MITHA with conventional THA, especially its effects on postoperative pain, recovery, and psychological distress in patients with ONFH.

Research objectives
This study aims to compare the effects of MITHA *vs* conventional THA in patients with ONFH and to further explore risk factors for postoperative negative emotions (NEs).

Research methods
The two surgical methods were comparatively analyzed, and the emotional state of the patients before and after surgery was investigated and analyzed using the regression model.

Research results
Patients undergoing MITHA had shorter operation time, less intraoperative bleeding and smaller incision length. Both groups of patients developed anxiety and depression before surgery, but some of them experienced emotional relief after treatment. Sex, postoperative pain score, and treatment cost were identified as risk factors affecting postoperative NEs of ONFH patients.

Research conclusions
MITHA is obvious advantageous over conventional THA in the treatment of ONFH, with short operation time and less bleeding. Sex, postoperative pain score, and treatment cost are risk factors that affect patients' postoperative mood. Targeted psychological counseling can effectively relieve the pressure of patients.

Research perspectives
A larger sample size and a long-term patient follow-up are needed to further determine the long-term effects of MITHA, as well as the depth and durability of the psychological impact on patients. Meanwhile, we need to better understand and deal with patients' postoperative psychological problems to improve the overall effectiveness of treatment.

FOOTNOTES

Author contributions: Yu WX and Cai YZ contributed to the study conception and design, drafting manuscript, data analysis and interpretation; Yu WX, Hao YQ, Lu C, Li H and Cai YZ contributed to the study conception, critical revision of article for important intellectual content; Yu WX and Cai YZ contributed to the study conception and design, critical revision of article for important intellectual content.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data for this study can be obtained from the corresponding author upon request at bonny17173@163.com.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of enhanced extracorporeal counterpulsation combined with atorvastatin in the treatment of cognitive impairment after stroke

Yan Duan, Hui-Xia Tang

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Abstract

BACKGROUND

Cerebral apoplexy patients are prone to cognitive impairment, and it is very important to choose appropriate treatment methods to improve their cognitive impairment after stroke.

AIM

To evaluate the effects of enhanced external counterpulsation (EECP) in conjunction with atorvastatin on cognitive function, neurotransmitter levels, and the repair of brain tissue damage in patients with cognitive impairment due to stroke.

METHODS

In this retrospective study, data from 60 patients with poststroke cognitive impairment due to stroke who were treated in our hospital from February 2021 to July 2022 were analyzed and divided into a treatment group (n = 30) and a control group (n = 30) according to the different nursing methods applied. Patients in the treatment group received EECP in addition to atorvastatin, while those in the control group received atorvastatin alone. Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and activities of daily living (ADL) scale scores were compared between the two groups. Additionally, the two groups were compared in terms of serum acetylcholine (ACh), acetylcholinesterase (AChE), nitric oxide (NO), endothelin-1 (ET-1), β2-microglobulin (β2-MG), glial fibrillary acidic protein (GFAP), and visinin-like protein 1 (VILIP-1) in the serum. Blood flow measurements from the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) were compared between the two groups before and after treatment, and the pulsatility index (PI) and resistance index (RI) of each artery were determined.

RESULTS

MMSE, MoCA, and ADL scores all improved in both groups following treatment, with the study group showing more improvement than the control group ($P < 0.05$). After treatment, there were statistically significant increases in both ACh and NO levels, whereas decreases occurred in AChE, ET-1, β2-MG, VILIP-1, and GFAP, levels and the PI and RI of the left-ACA, right-ACA, left-MCA, right-MCA, left-PCA, and right-PCA. The study group showed greater gains in all metrics than the control group ($P < 0.05$).

CONCLUSION

EECP combined with atorvastatin is effective in the treatment of cognitive impairment after stroke and can effectively improve the cognitive function, neurotransmitter levels, and brain tissue damage status of patients.

Key Words: Enhanced extracorporeal counterpulsation; Atorvastatin; Cognitive impairment after stroke; Neurotransmitters; Brain tissue damage status

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Core Tip: Enhanced extracorporeal counterpulsation and atorvastatin are widely used in the treatment of stroke patients with cognitive impairment, but the effect of enhanced counterpulsation combined with atorvastatin on cognitive function of stroke patients with cognitive impairment has not been discussed. The objective of this study was to compare the efficacy of enhanced external counterpulsation combined with atorvastatin *vs* atorvastatin alone in the treatment of post-stroke cognitive impairment. Combined therapy is better than atorvastatin therapy alone.

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INTRODUCTION

A patient's quality of life is drastically altered after suffering a stroke, which is an acute cerebrovascular event that can result in brain ischemia, hypoxic damage, and neurological abnormalities as well as sequelae such as language dysfunction, limb malfunction, and cognitive impairment. Cognitive impairment after stroke is caused by degenerative diseases resulting from neural tissue ischemia. Therefore, patients with cognitive impairment following a stroke may achieve some improvement in their clinical symptoms with clinical therapy for nutritional neuropathy, improvement of microcirculation, and hemorheology, along with physical exercise[1,2]. Safe, effective, and noninvasive, enhanced external counterpulsation (EECP) is a mechanical circulatory aid method commonly employed in the treatment of coronary heart disease and angina pectoris. Multiple recent studies have demonstrated the efficacy of EECP in treating ischemic cerebrovascular disease, sleep disturbances, and psychological and psychiatric diseases[3,4]. The mechanism of EECP is to increase both the arterial and venous return of both lower limbs, increase coronary blood flow, and improve the perfusion of the heart, brain, kidneys, and other organs[5]. Statins, which are hydroxymethylglutaryl coenzyme A reductase inhibitors, can significantly boost patients' cognitive performance and postpone disease progression[6] through their anti-inflammatory, antithrombotic, endothelium-protective, and antioxidant properties. The purpose of this research was to examine the effects of EECP in conjunction with atorvastatin on cognitive performance, neurotransmitter levels, and recovery from brain tissue damage in patients with poststroke cognitive impairment. The findings are detailed below.

MATERIALS AND METHODS

General information

Data from 60 patients with poststroke cognitive impairment due to stroke who were treated in our hospital from February 2021 to July 2022 were analyzed, and the patients were divided into a treatment group ($n = 30$) and a control group ($n = 30$) according to the different nursing methods applied. There were 21 men and 9 women in the study group, with ages ranging from 49 to 74 (mean = 61.40, SD = 5.59) years; the average duration since stroke onset was 6.30 ± 1.62 mo, and the average duration since cognitive impairment onset was 5.57 ± 1.14 mo. In the control group, the age ranged from 49 to 73 years, with a mean of 60.30 ± 5.84 years. There were 19 men and 11 women in the control group; the mean duration since stroke onset was 6.50 ± 1.28 mo, and the mean duration since the onset of cognitive impairment was 3.75 ± 0.78 mo. Overall, there was little to no difference in these data between the two groups ($P > 0.05$). All protocols in this study were approved by the ethics committee of the Shengjing Hospital of China Medical University and abided by the ethical guidelines of the Declaration of Helsinki. The ethics committee waived the requirement for informed consent.

Diagnostic criteria

All patients were diagnosed with stroke by imaging examination, and color ultrasound examination showed that there was a mural thrombus in the bilateral carotid arteries. The patients were diagnosed with mild cognitive impairment as described in the study of Ismail *et al*[7]: (1) All imaging examinations showed findings in accordance with the diagnostic criteria for stroke; (2) Progressive impairment of cognitive function; (3) Mild memory impairment; (4) Ability to continue daily life; and (5) Cognitive impairment less severe than the threshold for a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders[8]. Reduced capacity to orient oneself, recognize objects, and express oneself in language served as the primary clinical indications.

Inclusion criteria

(1) Imaging findings, physical examination findings, and a thorough review of the patient's medical history all corroborated the diagnosis, which matched all of the criteria laid forth in the Diagnostic Essentials of Various Cerebrovascular Diseases[9]; (2) Absence of any life-threatening organ malfunction; and (3) Voluntary participation in the research.

Exclusion criteria

(1) Neurological disease, such as Alzheimer's disease, Parkinson's disease, or epilepsy; (2) History of brain trauma; (3) Previous stroke or stroke-like event; (4) Existing mental disability before the stroke; and (5) Severe anxiety, depression, or other mental illness.

Methods

Atorvastatin was used in conjunction with EECP to treat patients in the research group (Pfizer Pharmaceutical Co., Ltd., National Drug Approval No.: H20051408). Patients in the control group were given only atorvastatin. Oxygen saturation was tracked using an EECP instrument (a PECP/TM) to measure EECP. The machine was first warmed for approximately 10-15 min. After the patient was positioned in an appropriate posture for treatment, sandpaper was used to smooth the skin around the electrode connection site, and alcohol was used to disinfect the immediate area. The white, red, and black electrodes were fixed under the left clavicle or near the manubrium, the apex of the heart, the upper right abdomen, or the lower right rib. Then, a finger pulse oximeter was placed on a finger of the right hand of the patient, ensuring that the electrode was in a position free from or minimally affected by vibration, the red and white electrodes were not too close, and the electrode position did not affect the inflatable cuff. The standard inflation pressure ranged from 0.025 to 0.045 MPa, with adjustments made during the operation based on the patient's response to the pressure. At the end of treatment, the finger pulse oximeter was removed, the inflatable cuff was unfastened, the electrode leads and electrodes were removed, and the patient was helped in tidying up his or her clothes and leaving the counterpulsation bed. The patient was required to remain under observation for 10 min without any discomfort before leaving. The treatment was performed once a day, 1 h/session, 6 d a week for 6 consecutive weeks, for a total of 36 sessions. Atorvastatin (20 mg) was given once daily for 24 wk.

Observational indexes

Clinical data of patients in the two groups were collected, and the Mini-Mental State Examination (MMSE)[10], Montreal Cognitive Assessment (MoCA)[11] and activities of daily living (ADL)[12] scores were compared between the two groups. Serum acetylcholine (ACh), acetylcholinesterase (AChE), nitric oxide (NO), endothelin-1 (ET-1), β2-microglobulin (β2-MG), visinin-like protein-1 (VILIP-1) and glial fibrillary acidic protein (GFAP) levels were compared between the two groups. The blood flow conditions of the bilateral anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) were compared between the two groups before and after treatment. The pulsatility index (PI) and resistance index (RI) of each artery were calculated according to the blood flow velocity of the left and right arteries during the peak systolic period (Vs), end-diastolic blood velocity (Vd) and average blood flow velocity (Vm), with PI = (Vs-VD)/Vm, and RI = (Vs-VD)/Vs.

The MMSE includes five different elements, with a total of 30 items and a total score of 30 points. The better the patient's mental condition, the higher the score. The total possible score on the MoCA is 30 points, and a MoCA score < 26 points indicates that the patient has cognitive impairment. The total possible score on the ADL scale is 100 points, and the higher the score, the better the patient's daily living ability. The abbreviations for the cerebral arteries are left ACA (LACA), right ACA (RACA), left MCA (LMCA), right MCA (RMCA), left PCA (LPCA), and right PCA (RPCA).

Statistical methods

SPSS 20.0 was employed for processing and analyzing the data. The values for the measurements are presented as "mean ± SD". The *t* test for independent samples was used to evaluate differences between the groups. Within-group comparisons of pre- and posttreatment values were performed using the paired *t* test. The χ^2 test was used to make comparisons, with count data being reported as frequencies and category ratios. $P < 0.05$ was considered to indicate a statistically significant difference.

Table 1 Comparison of Mini-Mental State Examination, Montreal Cognitive Assessment and activities of daily living scores between the two groups (mean ± SD, points)

Group	MMSE score		MoCA score		ADL score	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 30)	20.63 ± 2.94	26.80 ± 2.59[a]	19.50 ± 2.84	26.77 ± 2.08[a]	45.00 ± 4.78	63.70 ± 6.25[a]
Control group (n = 30)	19.73 ± 3.10	24.97 ± 3.29[a]	19.70 ± 1.60	24.70 ± 2.42[a]	45.97 ± 4.62	57.40 ± 4.99[a]
P value	0.253	0.020	0.738	0.001	0.429	< 0.001
t value	1.154	2.400	0.336	3.545	0.797	4.314

[a]P < 0.05, compared with the same group before treatment.
MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; ADL: Activities of daily living.

Table 2 Comparison of cholinergic system component levels between the two groups (mean ± SD, nmol/mL)

Group	ACh		AChE	
	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 30)	10.96 ± 2.84	22.53 ± 2.49[a]	16.53 ± 2.09	8.26 ± 0.89[a]
Control group (n = 30)	10.54 ± 2.99	15.20 ± 1.66[a]	16.92 ± 2.75	12.36 ± 1.17[a]
t value	0.570	13.412	0.616	15.308
P value	0.571	< 0.001	0.540	< 0.001

[a]P < 0.05, compared to the same group before treatment.
Ach: Acetylcholine; AChE: Acetylcholinesterase.

RESULTS

Comparison of MMSE, MoCA, and ADL scores between the two groups

There were no statistically significant differences between the groups in the pretreatment MMSE, MoCA, or ADL scores (P > 0.05). The treatment group showed statistically significant (P < 0.05) improvements in the MMSE, MoCA, and ADL scores after treatment compared to the control group, as shown in Table 1 and Figure 1A.

Comparison of neurotransmitter levels between the two groups

There were no statistically significant differences in the pretreatment ACh or AChE level between the two groups. In both groups, the ACh level increased after therapy, while the AChE level decreased (P < 0.05). There were statistically significant (P < 0.05) improvements in all indices in the experimental group that were not present in the control group, as shown in Table 2 and Figure 1B.

Comparison of vascular endothelial function markers between the two groups

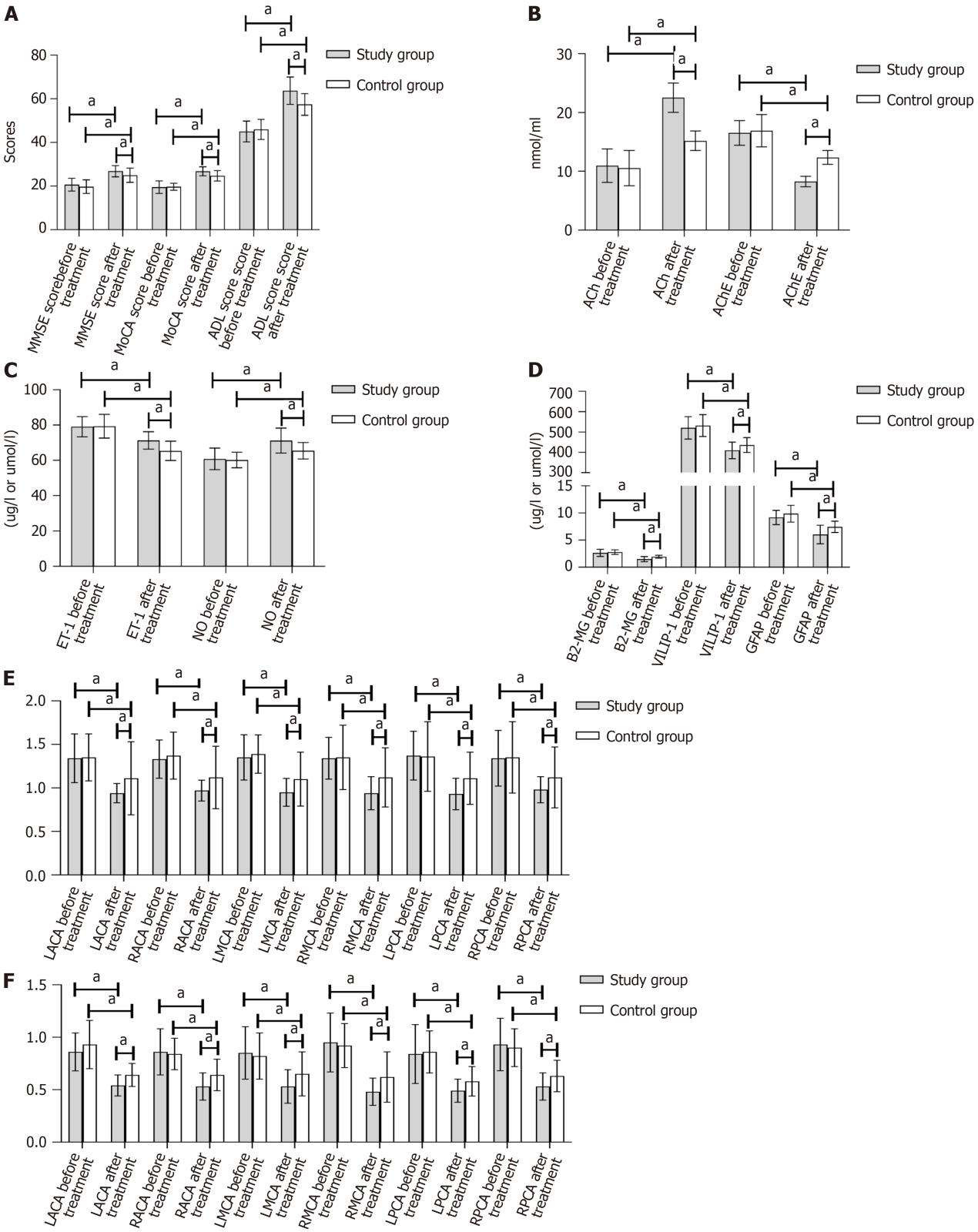
There was no significant change in the ET-1 or NO level between the two groups before treatment (P > 0.05). After therapy, the ET-1 level in both groups decreased, and the NO level increased. The study group showed significantly (P < 0.05) greater improvement than the control group in all areas, as shown in Table 3 and Figure 1C.

Evaluation of serum levels of β2-MG, VILIP-1, and GFAP between the two groups

There were no significant variations in the β2-MG, VILIP-1, or GFAP levels between the two groups prior to therapy (P > 0.05). After treatment, the β2-MG, VILIP-1, and GFAP levels decreased in both groups, with significantly lower levels in the study group (P < 0.05), as shown in Table 4 and Figure 1D.

Comparison of PI values of the cerebral vasculature between the two groups

The PI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA were not significantly different between the two groups before treatment (P > 0.05). As expected, therapy resulted in a reduction of pretreatment PI values in all examined vessels (LACA, RACA, LMCA, RMCA, LPCA, and RPCA) in both groups, with the study group showing significantly (P < 0.05) lower PI levels than the control group, as presented in Table 5 and Figure 1E.



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Figure 1 Comparison of the level of each observation index between the two groups. A: Comparison of neurotransmitter levels between the two groups; B: Comparison of neurotransmitter levels between the two groups; C: Comparison of vascular endothelial function markers between the two groups; D: Evaluation of serum levels of β2-microglobulin, visinin-like protein 1, and glial fibrillary acidic protein between the two groups; E: Comparison of pulsatility index values of the cerebral vasculature between the two groups; F: Analyzing the difference in resistance index values of the cerebral vessels between the two groups. MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; ADL: Activities of daily living; Ach: Acetylcholine; AChE: Acetylcholinesterase; NO: Nitric oxide; ET-1: Endothelin-1; β2-MG: β2-microglobulin; GFAP: Glial fibrillary acidic protein; VILIP-1: Visinin-like protein 1; LACA: Left-anterior cerebral artery; RACA: Right-anterior cerebral artery; LMCA: Left-middle cerebral artery; RMCA: Right-middle cerebral artery; LPCA: Left-posterior cerebral artery; RPCA: Right-posterior cerebral artery. $^{a}P < 0.05$.

Table 3 Comparison of vascular endothelial function markers between the two groups (mean ± SD, d)

Group	ET-1 (μg/L)		NO (μmol/L)	
	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 30)	79.02 ± 5.77	71.29 ± 4.90[a]	60.81 ± 6.13	71.19 ± 7.08[a]
Control group (n = 30)	79.32 ± 6.70	65.40 ± 5.45[a]	60.19 ± 4.40	65.45 ± 4.64[a]
P value	0.854	< 0.001	0.655	0.001
t value	0.185	4.400	0.450	3.709

[a]P < 0.05, compared to the same group before treatment.
NO: Nitric oxide; ET-1: Endothelin-1.

Table 4 Comparison of serum β2-microglobulin, glial fibrillary acidic protein, and visinin-like protein 1 concentrations between the two groups (mean ± SD)

Group	B2-MG (mg/L)		VILIP-1 (ng/L)		GFAP (mg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 30)	2.64 ± 0.65	1.49 ± 0.48[a]	520.59 ± 55.39	409.67 ± 40.77[a]	9.17 ± 1.32	6.04 ± 1.70[a]
Control group (n = 30)	2.79 ± 0.42	1.93 ± 0.28[a]	531.47 ± 54.03	435.83 ± 37.09[a]	9.87 ± 1.56	7.44 ± 1.06[a]
P value	0.294	< 0.001	0.444	0.012	0.064	< 0.001
t value	1.061	4.339	0.771	2.599	1.888	3.817

[a]P < 0.05 compared to the same group before treatment.
β2-MG: β2-microglobulin; GFAP: Glial fibrillary acidic protein; VILIP-1: Visinin-like protein 1.

Analyzing the difference in RI values of the cerebral vessels between the two groups

The RI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA were similar in the two groups before treatment (P > 0.05). Treatment resulted in a substantial (P < 0.05) reduction in the RI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA in both groups, as shown in Table 6 and Figure 1F.

DISCUSSION

The degree of cognitive impairment in stroke patients is strongly correlated with their prognosis, and elderly individuals are especially prone to cognitive impairment as a sequela of cerebral infarction. Therefore, it is crucial to find efficient ways to reduce stroke patients' cognitive impairment. According to relevant studies, atorvastatin serves antioxidant and antithrombotic functions and protects vascular endothelial function. It can play a direct role in protecting nerves, reducing the abundance of macrophages in atherosclerotic plaques, enhancing the integrity of fibrous plaque caps, inhibiting vascular inflammation, protecting the vascular endothelium, and inhibiting cognitive impairment after a stroke caused by vascular factors. EECP is a safe and cost-effective treatment that is mainly suitable for the treatment of coronary heart disease and angina pectoris. Numerous investigations conducted recently have demonstrated that EECP significantly affects ischemic cerebrovascular disorders and heart failure[13,14]. According to a prior study, EECP can reduce the clinical symptoms of coronary artery disease by enhancing vascular endothelial function[15]. EECP is an important means of cardiovascular auxiliary circulation that can simultaneously increase the arterial and venous return of both lower limbs and improve coronary blood flow. Patients' diastolic blood pressure and cardiac output as well as blood perfusion to the heart, brain, kidneys, and other organs can all be improved by wrapping balloon sleeves around the thighs, calves, and buttocks and then inflating and deflating the balloons using an air supply system. EECP has been shown to enhance arterial blood flow, increase blood perfusion in brain tissue, improve brain cell metabolism, and facilitate neurological function recovery[16]. Numerous clinical trials have demonstrated that EECP is able to successfully increase blood flow to ischemic areas, restore nerve cell activity, and facilitate the opening of collateral circulation in the ischemic penumbra[17,18].

This research compared the effects of EECP combined with atorvastatin to those of atorvastatin alone between two groups. The results indicated that after therapy, the MMSE, MoCA, and ADL scores in the study group improved more than those in the control group (P < 0.05). These findings demonstrate that the combined application of EECP and atorvastatin might be more effective than atorvastatin alone in enhancing patients' cognitive function and daily living abilities and that such enhancements could serve as direct indicators of the efficacy of therapy. The endothelium lining

Table 5 Comparison of pulsatility index values of cerebral vessels between the two groups (mean ± SD)

Group	LACA		RACA		LMCA		RMCA		LPCA		RPCA	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 30)	1.34 ± 0.28	0.94 ± 0.11[a]	1.33 ± 0.22	0.97 ± 0.12[a]	1.35 ± 0.26	0.95 ± 0.16[a]	1.34 ± 0.24	0.94 ± 0.19[a]	1.37 ± 0.28	0.93 ± 0.18[a]	1.34 ± 0.32	0.98 ± 0.15[a]
Control group (n = 30)	1.35 ± 0.27	1.11 ± 0.42[a]	1.37 ± 0.27	1.12 ± 0.36[a]	1.39 ± 0.22	1.10 ± 0.31[a]	1.35 ± 0.37	1.12 ± 0.34[a]	1.36 ± 0.40	1.11 ± 0.30[a]	1.35 ± 0.41	1.12 ± 0.35[a]
P value	0.832	0.040	0.536	0.049	0.490	0.024	0.905	0.013	0.857	0.007	0.983	0.047
t value	0.213	2.139	0.622	2.043	0.695	2.339	0.120	2.589	0.180	2.805	0.021	2.052

[a]P < 0.05 compared to the same group before treatment.

LACA: Left-anterior cerebral artery; RACA: Right-anterior cerebral artery; LMCA: Left-middle cerebral artery; RMCA: Right-middle cerebral artery; LPCA: Left-posterior cerebral artery; RPCA: Right-posterior cerebral artery.

Table 6 Comparison of the resistance index values of the cerebral vessels in the two groups (mean ± SD)

Group	LACA		RACA		LMCA		RMCA		LPCA		RPCA	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (n = 30)	0.86 ± 0.18	0.54 ± 0.10[a]	0.86 ± 0.22	0.53 ± 0.13[a]	0.85 ± 0.25	0.53 ± 0.16[a]	0.95 ± 0.28	0.48 ± 0.13[a]	0.84 ± 0.28	0.49 ± 0.11[a]	0.93 ± 0.25	0.53 ± 0.13[a]
Control group (n = 30)	0.93 ± 0.23	0.64 ± 0.11[a]	0.84 ± 0.15	0.64 ± 0.15[a]	0.82 ± 0.22	0.65 ± 0.21[a]	0.92 ± 0.21	0.62 ± 0.24[a]	0.86 ± 0.20	0.58 ± 0.14[a]	0.90 ± 0.18	0.63 ± 0.15[a]
P value	0.225	0.001	0.729	0.004	0.720	0.014	0.582	0.007	0.701	0.006	0.566	0.008
t value	1.226	3.661	0.349	3.033	0.360	2.547	0.553	2.847	0.386	2.864	0.578	2.750

[a]P < 0.05 compared to the same group before treatment.

LACA: Left-anterior cerebral artery; RACA: Right-anterior cerebral artery; LMCA: Left-middle cerebral artery; RMCA: Right-middle cerebral artery; LPCA: Left-posterior cerebral artery; RPCA: Right-posterior cerebral artery.

the blood vessels is vulnerable to oxidative damage, which can be caused by atherosclerosis. Atorvastatin is a commonly used lipid-lowering drug that stabilizes atherosclerotic plaques. EECP can play a role in increasing cerebral blood flow and perfusion and improving neural function, such that the combined application of these two treatments is more effective. Previous studies have also shown that EECP combined with conventional drugs can be used to treat poststroke cognitive impairment more effectively than the same drugs alone[19]. Learning and memory are two physiological processes that benefit greatly from the functioning of the central cholinergic system. AChE catalyzes the decomposition reaction that produces ACh, which binds to ACh receptors. Degeneration of cholinergic neurons is common in patients with cognitive impairment after stroke[20]. ACh can participate in neuronal activity and regulate synaptic plasticity. In this investigation, the improvement in ACh and AChE levels following therapy was larger in the study group than in the control group (P < 0.05). The treatment of cognitive impairment following a stroke, which may be connected to the management of AChE and ACh levels, is said to benefit significantly from the combination of EECP and atorvastatin. The vascular endothelium serves both barrier and endocrine functions. Dysfunction of vascular endothelial cells can lead to damage to the blood-brain barrier, causing toxic substances to accumulate around nerve cells; triggering inflammatory reactions; damaging brain white matter, neuronal axons and synapses; and leading to cognitive impairment. Vascular endothelial damage, atherosclerosis, brain tissue damage, increased ET-1 expression, and decreased NO expression result in spasms of small cerebral vessels and damage to the nerve fiber network. It has been reported that the serum ET-1 and NO levels in patients with dementia are closely related to endothelial dysfunction of small cerebral vessels and can be used as a marker of endothelial dysfunction[21]. Patients with cognitive impairment following stroke showed significant improvement in ET-1 and NO levels in the treatment group compared to the control group, suggesting that combination therapy can increase the degree of vascular endothelial function more effectively than pharmacotherapy alone. Atorvastatin's lipid-lowering action, ability to mitigate atherosclerosis and protective effect on vascular endothelial function are all well documented. EECP has been shown to ameliorate cognitive impairment by normalizing systolic and diastolic vascular function, controlling vascular tension, and boosting endothelial function in blood vessels. Thus, when

applied in combination, they could play synergistic roles, resulting in an enhanced therapeutic effect.

All nucleated cells contain β2-MG, which might increase the risk of an inflammatory response and subsequent brain injury. With a negative effect on cognition, β2-MG has been linked to a host of serious health problems[22]. According to relevant studies, serum β2-MG levels are high in patients with cognitive impairment after stroke[23]. It has been shown that the expression level of VILIP-1, a small-molecule cytosolic protein typically dispersed in nerve cells, is positively linked with the presence of brain damage[24]. Serum levels of GFAP, an intermediate filament protein found in glial cells, are significantly elevated in those who have had a stroke and are experiencing cognitive impairment[25]. The fact that the levels of β2-MG, VILIP-1, and GFAP improved more in the study group than in the control group suggests that the combination therapy may promote the healing of damaged brain tissue in patients, which merits additional investigation into the specific mechanism of action. Patients with poststroke cognitive impairment who received combination therapy showed greater improvements in the PI and RI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA than those who received atorvastatin therapy alone. This is because of the synergistic impact of atorvastatin's lipid-lowering and antithrombotic effects and the capacity of EECP to increase cerebral blood flow perfusion.

CONCLUSION

In conclusion, EECP combined with atorvastatin can effectively improve cognitive function, daily living ability, vascular endothelial function, neural function, and cerebral blood flow in patients with poststroke cognitive dysfunction, indicating the clinical value of this combination. A limitation of this study is that it was a retrospective study, and the number of cases that could be included in the observation was small, which may have led to bias in the results. In the future, a prospective multicenter study with a larger sample should be conducted to further verify the results of this study.

ARTICLE HIGHLIGHTS

Research background

The research background is the discussion on the treatment of patients with cognitive dysfunction after stroke. The current research status is that atorvastatin is widely used to treat cognitive impairment after stroke, and the research significance is to provide a new treatment plan for cognitive impairment after stroke and improve clinical efficacy.

Research motivation

With the treatment of stroke patients with cognitive dysfunction as the research topic, more effective treatment plans need to be explored to improve the prognosis of stroke patients with cognitive dysfunction. The significance of this study is to affirm the better treatment of cerebral stroke patients with cognitive dysfunction, and promote the innovation of clinical treatment of cerebral stroke cognitive endometrial methods.

Research objectives

The objective of this study was to compare the therapeutic effect of different treatment methods and to observe the advantages of enhanced external counterpulsation (EECP) combined with atorvastatin over atorvastatin alone. In this study, enhanced *in vitro* rebuttal combined with atorvastatin was effective in the treatment of cognitive dysfunction in stroke patients, including cognitive function, ability of daily living, vascular endothelial function, nerve function and cerebral blood flow, confirming that the combined treatment has good clinical effects and providing a new reference for the treatment of cognitive dysfunction in stroke patients in the future.

Research methods

The clinical data of the patients were analyzed retrospectively and grouped according to different treatment methods. Then, independent sample *t* test, paired sample *t* test and χ^2 test were used to statistically analyze the general data of the two groups, including mental state, cognitive function, daily living ability score, neurotransmitter level, vascular endothelial function index level, cognitive-related index and cerebral blood flow index before and after treatment. The feature of retrospective study is to explore the cause through the results, and it is easier to obtain the case data.

Research results

EECP combined with atorvastatin can significantly improve cognitive function, mental state, ability of daily living, vascular endothelial function, nerve function and cerebral blood flow in the treatment of stroke patients with cognitive dysfunction, which provides a new treatment method for the treatment of stroke patients with cognitive dysfunction and requires further prospective exploration. To further verify the effectiveness of this treatment method.

Research conclusions

Vascular endothelial dysfunction can lead to impairment of the blood-brain barrier, leading to cognitive dysfunction. Therefore, attention should be paid to the effect of treatment on vascular endothelial function. Based on the better treatment effect of EECP combined with atorvastatin, the more effective treatment scheme should be selected in clinic.

Research perspectives

Biological indicators can effectively reflect the severity of the patient's disease, and the effect of treatment regimen on the level of novel biomarkers in patients with post-stroke cognitive dysfunction needs to be further explored.

FOOTNOTES

Author contributions: Duan Y initiated the project, designed the experiment and conducted clinical data collection; Tang HX performed postoperative follow-up and recorded data, conducted a number of collation and statistical analysis, and wrote the original manuscript; both authors reviewed and approved the paper; and all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University.

Informed consent statement: The ethics committee waived the requirement for informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All data generated or analyzed during this study are included in this published article.

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ORIGINAL ARTICLE

Retrospective Study

Value of Chuanjin Qinggan decoction in improving the depressive state of patients with herpes zoster combined with depression

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Abstract

BACKGROUND

Western medicine is beneficial for the recovery of neurological function in patients with depression, but some patients experience side effects such as headaches, dizziness, nausea, gastrointestinal symptoms, insomnia, and cardiac dysfunction. In recent years, integrative medicine has achieved positive results in the treatment of various diseases.

AIM

To study Chuanjin Qinggan decoction combined with selective serotonin reuptake inhibitors (SSRIs) in patients with herpes zoster complicated by depression.

METHODS

Patients with herpes zoster complicated by depression who were treated at the Yantai Hospital of Traditional Chinese Medicine from January 2021 to December 2022 were retrospectively selected as research participants. Among them, 43 patients with herpes zoster complicated by depression who received SSRI treatment between January and December 2021 were assigned to the Western medicine group, while those who received combined treatment of traditional Chinese and Western medicine between January and December 2022 were assigned to the combined group. Both groups were treated for eight weeks. The degree of pain, effect of herpes zoster treatment, degree of improvement in depressive symptoms, serum neurotransmitter levels, sleep quality, and occurrence of adverse reactions were compared between the two groups.

RESULTS

We found that after eight weeks of drug treatment, the two treatment schemes achieved differing efficacy. In further comparison, we found that, compared with

patients treated with SSRIs alone, patients treated with Chuanjin Qinggan decoction combined with SSRIs showed more significant improvement in depression and a greater increase in dopamine and 5-hydroxytryptamine levels after treatment ($P < 0.05$). Patients treated with Chuanjin Qinggan decoction combined with SSRIs also experienced lower pain, better treatment efficacy for herpes zoster, better sleep quality, and a lower incidence of adverse reactions compared to those treated with SSRIs alone ($P < 0.05$). All minor adverse reactions occurring during treatment were resolved after symptomatic treatment.

CONCLUSION

The treatment scheme of Chuanjin Qinggan decoction combined with SSRIs can improve the psychological state of patients with herpes zoster complicated by depression and alleviate adverse reactions.

Key Words: Chuanjin Qinggan decoction; Selective 5-hydroxytryptamine reuptake inhibitor; Herpes zoster; Depression; Sleep quality; Adverse reaction

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Core Tip: Chuanjin Qinggan decoction is an important decoction composed mainly of Ligusticum chuanxiong Hort, Curcuma, and Sedum rosea. There is a synergistic effect between the active ingredients in Chuanjin Qinggan decoction which helps to reduce neurological damage and improve the depressive state of patients by providing raw materials and energy for protein and nucleic acid synthesis in brain tissue. This study confirmed that the treatment scheme of Chuanjin Qinggan decoction combined with selective serotonin reuptake inhibitors can effectively improve the depressive state of patients with herpes zoster complicated by depression.

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INTRODUCTION

Herpes zoster is an acute herpetic skin disease characterized by clusters of blisters on the skin and burning pain[1]. It is characterized by the sudden occurrence of these blisters arranged in a ribbon along one side of the peripheral nerve distribution area, accompanied by tingling and lymphadenopathy[2]. Herpes zoster usually occurs in spring or autumn, and older adults constitute the majority of the affected population[3]. Most patients with herpes zoster do not experience recurrence after illness, although recurrence sometimes occurs[4]. Herpes zoster can cause burning, knife-cutting, or electric shock-like pain, with erythema and blisters on the skin's surface. It affects a patient's appearance and can cause physical and mental harm. If patients with herpes zoster do not receive effective treatment for an extended period, they may experience different degrees of depressive symptoms as the pain progresses.

Recent studies suggest that secondary depression in patients with herpes zoster is related to postherpetic neuralgia (PHN)[5,6]. PHN is an intractable neuropathic pain syndrome secondary to herpes zoster that causes the irreversible destruction of nerve fibers. When PHN destroys the neural pathways regulating emotion, it leads to the dysfunction of monoamine neurotransmitters. If the lesion site involves the thalamus, basal ganglia, amygdala, frontal lobe, hippocampus, or interconnected fibers, it can damage serotonergic neurons and reduce the level of 5-hydroxytryptamine (5-HT), eventually leading to depression[7]. The World Health Organization estimates that by 2030, depression may rank first in the global burden of disease[8]. Herpes zoster combined with depression brings a great psychological burden to patients and may reduce their medication compliance and rehabilitation process.

Selective 5-hydroxytryptamine reuptake inhibitors (SSRIs) are safe and can effectively regulate the concentration of monoamine transmitters in the body and reduce depression-like symptoms. They are the first-line antidepressants recommended by various guidelines. A previous study showed that SSRIs are beneficial for the recovery of neurological function in patients with depression[9]. However, some patients experience side effects such as headaches, dizziness, nausea, gastrointestinal symptoms, insomnia, and cardiac dysfunction. SSRIs have also been shown to affect the cardiac and cerebral vessels of patients[10]. Compared to patients with depression alone, patients with herpes zoster combined with depression are more likely to have aggravated depressive symptoms due to physiological pain. Therefore, there is an urgent need to develop a treatment plan that can relieve physiological pain and improve the psychological state of patients with herpes zoster and depression.

According to traditional Chinese medicine, depressive symptoms are mainly related to the dysfunction of the five internal organs and poor emotions. The depressive symptoms of patients with herpes zoster include depression, chest and flank fullness, and irritability caused by physiological and psychological pressure. Chuanjin Qinggan decoction promotes Qi, relieves depression, maintains the liver, clears heat, and detoxifies. However, the specific efficacy of Chuanjin Qinggan decoction combined with SSRIs in treating herpes zoster complicated by depression remains unclear.

In recent years, integrative medicine has achieved positive results in the treatment of various diseases. Since 2022, our hospital has actively attempted integrated traditional Chinese and Western medicine therapy for patients with herpes zoster complicated by depression, achieving good results. This study aims to explore the effect of Chuanjin Qinggan decoction combined with SSRIs in patients with herpes zoster complicated by depression.

MATERIALS AND METHODS

Patients

Patients with herpes zoster complicated by depression who were treated at the Yantai Hospital of Traditional Chinese Medicine between January 2021 and December 2022 were retrospectively selected as research participants. Inclusion criteria were as follows: (1) Meeting the relevant diagnostic criteria for herpes zoster[11]; (2) Hamilton Depression Scale (HAMD) score > 8[12]; (3) age ranging from 30 to 75 years; (4) complete clinical data required for this study; and (5) no history of depression before from the onset of herpes zoster. The exclusion criteria were as follows: (1) Patients with organic mental disorders; (2) patients with significant organ dysfunction; (3) patients with congenital cognitive dysfunction; (4) patients with less than one course of treatment; and (5) patients with allergies to the drugs used in this study.

Grouping and treatment

Eighty-six patients were finally included in the study, and all patients were treated with the same method: acyclovir tablets (specification: 0.1 g/tablet), 0.4 g each time, five times a day; acyclovir cream applied externally, once every two hours, 4-6 times a day. The treatment lasted for two weeks. According to the treatment plan for depression, the patients were divided into Western medicine and combination groups.

Western medicine group: Patients with herpes zoster complicated by depression who received SSRIs between January and December 2021 were included in the Western medicine group. SSRIs include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. The following SSRIs and dosages were used by the patients in this study: The starting dose of sertraline tablets (specification: 50 mg/tablet) was 50 mg/d, administered after breakfast. Clinicians can adjust the drug dose within 7-14 d according to the actual condition of the patient, and the adjustment range is 50-150 mg/d. The starting dose of the enteric-coated paroxetine tablets (20 mg/tablet) was 20 mg/d, taken after breakfast. Clinicians can adjust the drug dose within 7-14 d according to the actual condition of the patient, and the adjustment range is 20-60 mg/d. The starting dose of escitalopram tablets (20 mg/tablet) was 10 mg/d, taken after breakfast. Clinicians can adjust the drug dose within 7-14 d according to the actual condition of the patient, and the adjustment range is 10-20 mg/d. The total treatment duration was eight weeks.

The combination group included patients with herpes zoster complicated by depression who received combined treatment of traditional Chinese and Western medicines between January and December 2022. The Western medicine treatment method was the same as that used in the Western medicine group. The traditional Chinese medicine treatment was Chuanjin Qinggan decoction: Ligusticum chuanxiong Hort (10 g), Curcuma (10 g), Rhodiola (15 g), Bupleurum (12 g), Gardenia (10 g), Paeonia alba (12 g), Rehmannia glutinosa (20 g), Peony bark (10 g), Poria cocos (20 g), Alisma orientalis (10 g), Acanthopanax senticosus (15 g), Schisandra (15 g), Albizzia julibrissin bark (15 g), Glycyrrhiza uralensis (6 g), and Forsythia suspensa (10 g). They were added or removed according to the patient's condition and decocted in 500 mL of water. This was administered once in the morning and evening for 14 d as a course of treatment for four consecutive courses (eight weeks).

Outcome measures

Patient depression before and after treatment was the primary outcome measure. The HAMD scale was used to evaluate the depression status of patients one week before treatment, four weeks after treatment, and eight weeks after treatment. The HAMD scale used in this study has 17 items, of which a score ≤ 7 points indicates normal; the higher the score, the more severe the participant's depression.

The secondary outcome measures were as follows. (1) Patients' pain before and after treatment: The visual analog scale (VAS)[13] was used to evaluate the degree of pain in patients one week before and at the end of treatment. The VAS scores range from 0 to 10, with 0 indicating no pain and 10 indicating severe pain; (2) The effectiveness of herpes zoster treatment: remarkable effect: more than 70% of the rash disappeared, and the pain symptoms were alleviated; effective: 30%-70% of the rash disappeared, and the pain symptoms were alleviated; ineffective: less than 30% of the rash disappeared, and the pain did not change or worsened; (3) Neurotransmitter levels: The serum levels of dopamine (DA) and 5-HT were monitored before and after treatment; (4) Sleep quality: The Pittsburgh Sleep Quality Index (PSQI)[14] was used to evaluate sleep quality. The PSQI scale was compiled by psychiatrists and scholars at the University of Pittsburgh with seven factors derived from clinical practice; each factor had a score range of 0 to 3 points. The final PSQI score was the sum of the seven factor scores. The scale's total score was 21 points; the higher the total score, the worse the sleep quality; and (5) Patients' adverse reactions during treatment were recorded, including headache, blurred vision, nausea, vomiting, and cognitive dysfunction.

Statistical analysis

SPSS 26.0 and GraphPad 9.0 were used for statistical analysis. The statistical data were expressed by frequency and percentage, and the χ^2 test was used for comparison between groups (the rank sum test was used for the count data with hierarchical characteristics). The measurement data that conform to and do not conform to the normal distribution are

expressed by the mean (standard deviation) and median (P25, p75), respectively. The data that conformed used a *t*-test and repeated-measures analysis of variance for comparison between groups, and the data that did not conform used the Mann-Whitney *U* test. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical characteristics of study participants

To ensure the comparability of different drug treatment results, the baseline data of the two groups of patients were compared. After comparison, the statistical analysis showed no significant differences in the baseline data of the two groups of patients receiving different drugs, such as sex, age, duration of herpes zoster, residence, and years of education ($P > 0.05$) (Table 1).

Comparison of the degree of pain

As shown in Table 2, after eight weeks of treatment, the overall VAS scores of the two groups decreased compared to those before treatment, and the VAS scores of patients treated with Chuanjin Qinggan decoction combined with SSRIs decreased more significantly ($P < 0.05$).

Comparison of the therapeutic effectiveness against herpes zoster

In the comparison of the therapeutic effects of the two treatment groups against herpes zoster, it was found that the effect observed in patients treated with Chuanjin Qinggan decoction combined with SSRIs was higher than that in patients treated with SSRIs alone, the ineffective rate was lower than that in patients treated with SSRIs alone, and there was a significant difference in the overall efficacy between the two groups ($P < 0.05$) (Table 3).

The changing trend of patients' depression

As shown in Figure 1, after eight weeks of treatment, the overall HAMD score of patients in both groups decreased compared to that before treatment, and the decrease in HAMD score of patients treated with Chuanjin Qinggan decoction combined with SSRIs was more significant ($P < 0.05$).

Effects of different treatment schemes on neurotransmitter levels in patients

Both treatment regimens improved the serum DA and 5-HT levels of patients, and patients treated with Chuanjin Qinggan decoction combined with SSRIs showed a greater increase in DA and 5-HT levels (both $P < 0.05$) (Figure 2).

Effect of different treatment schemes on sleep quality of patients

Both treatment regimens reduced the PSQI score of patients, and the decrease in the PSQI score of patients treated with Chuanjin Qinggan decoction combined with SSRIs was more significant ($P < 0.05$) (Figure 3).

Occurrence of adverse reactions

Neither treatment method had adverse effects on cognitive function. A few patients experienced minor adverse reactions such as headaches, blurred vision, nausea, and vomiting, which were alleviated after symptomatic intervention. The overall incidence of adverse reactions in patients treated with Chuanjin Qinggan decoction combined with SSRIs was lower than that in patients treated with SSRIs alone ($P < 0.05$) (Table 4).

DISCUSSION

In addition to the core symptoms of depression such as low mood, reduced willpower, and reduced interest, patients with depression also have a severe inferiority complex accompanied by varying degrees of memory loss, sluggish thinking, irritability, and refusal to eat[15]. If the psychological state of a patient with depression cannot be improved for an extended period, the development of severe depression may lead to self-mutilation or even suicide. In recent years, with the development of social psychology, people have begun to pursue comprehensive physical and mental health. Given the negative effects of depression on patients' physiology and psychology, the treatment of depressive symptoms in patients with herpes zoster combined with depression is necessary to improve their well-being. Simultaneously, the treatment of depressive symptoms in patients with herpes zoster and depression can also reduce the burden on their families and society. Therefore, society and most medical workers attach great importance to the treatment of depressive symptoms in patients with herpes zoster combined with depression.

To understand the therapeutic effects of different treatment schemes in patients with herpes zoster complicated by depression, the clinical data of 86 patients were retrospectively analyzed. The results showed that although both treatment regimens could achieve efficacy, patients treated with Chuanjin Qinggan decoction combined with SSRIs showed more significant improvement in depression and a greater increase in DA and 5-HT levels after treatment compared to those treated with SSRIs alone. SSRIs exert antidepressant effects by inhibiting the resorption of 5-HT by the presynaptic membrane, and their efficacy in treating depression has been confirmed. The depressive symptoms of patients treated with SSRIs in this study also improved, similar to the results of previous studies. Findling *et al*[16]

Table 1 Clinical characteristics of study subjects [*n* (%)], M (P_{25}, P_{75})

Clinical characteristics	Western medicine (*n* = 43)	Combination (*n* = 43)	χ^2/t	*P* value
Sex			0.427	0.514
Man	26 (60.50)	23 (53.50)		
Woman	17 (39.50)	20 (46.50)		
Age (yr)	58.53 ± 5.16	59.12 ± 5.04	-0.528	0.599
Herpes zoster disease course (d)	5.00 (4.00, 6.00)	5.00 (4.00, 6.00)	-0.317	0.751
Residence			0.187	0.665
Town	19 (44.20)	21 (48.80)		
City	24 (55.80)	22 (51.20)		
Years of education			0.466	0.792
< 9	8 (18.60)	10 (23.30)		
9-12	24 (55.80)	21 (48.80)		
> 12	11 (25.60)	12 (27.90)		

Table 2 The pain scores between the two groups, M (P_{25}, P_{75})

Group	Pre-treatment	Post-treatment	*Z*	*P* value
Western medicine (*n* = 43)	7.00 (6.00, 8.00)	4.00 (4.00, 5.00)	-6.801	< 0.001
Combination (*n* = 43)	7.00 (6.00, 8.00)	4.00 (3.00, 4.00)	-7.960	< 0.001
Z	-0.448	-3.825		
P value	0.654	< 0.001		

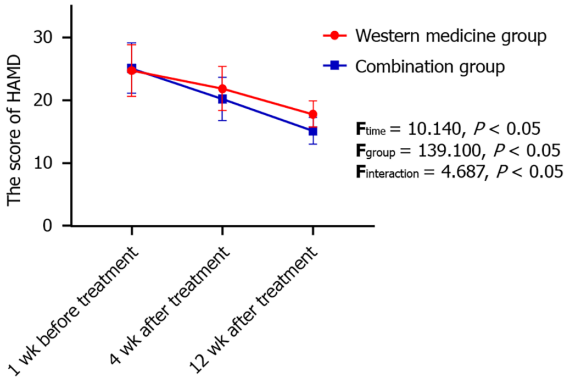
Table 3 Effectiveness of herpes zoster treatment, *n* (%)

Group	Remarkable effect	Effective	Ineffective
Western medicine (*n* = 43)	11 (25.58)	22 (51.16)	10 (23.26)
Combination (*n* = 43)	19 (44.19)	18 (41.86)	6 (13.95)
Z	-2.144		
P value	0.032		

Table 4 Comparison of adverse reactions produced by different treatment regimens, *n* (%)

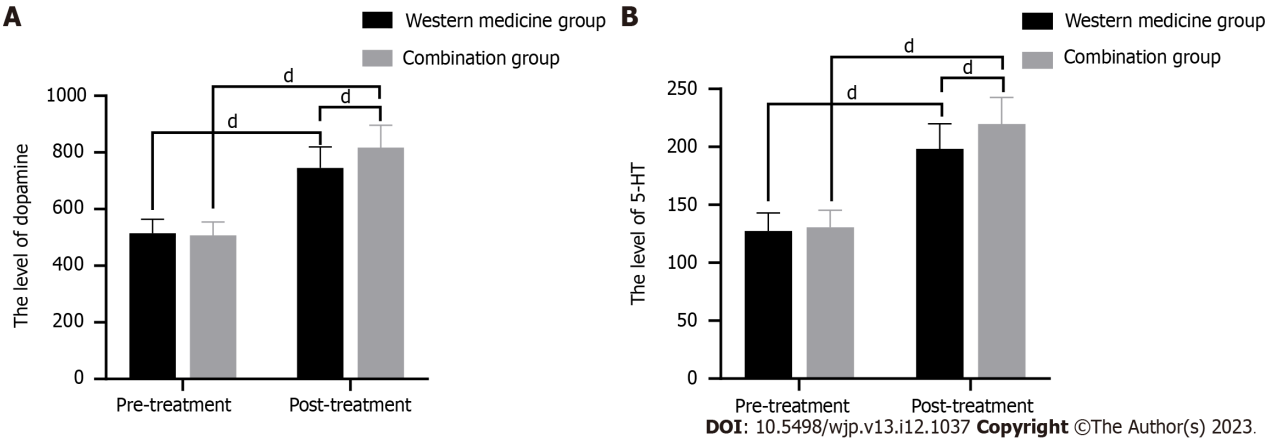
Group	Headache	Blurred vision	Nausea	Emesis	Others	Total
Western medicine (*n* = 43)	5 (11.63)	2 (4.65)	6 (13.95)	3 (6.98)	3 (6.98)	17 (39.53)
Combination (*n* = 43)	2 (4.65)	1 (2.33)	4 (9.30)	1 (2.33)	3 (6.98)	8 (18.60)
χ^2						4.568
P value						0.033

reported that SSRIs can achieve good efficacy in the treatment of depression in adolescents and adults. Fagiolini *et al*[17] also reported that SSRIs could improve depressive symptoms in patients with severe depression. DA is the most abundant catecholamine neurotransmitter in the brain (accounting for approximately 80% of the total). It controls various functions, such as motor activity, cognition, emotion, food intake, and endocrine regulation. Diseases such as Parkinson's disease, schizophrenia, and addictive behavior are all related to dopaminergic system dysfunction[18,19]. Abnormal function of the serotonin system is closely related to loss of appetite, sleep disorders, decreased activity, sexual dysfunction, endocrine dysfunction, depression, and anxiety[20]. Chuanjin Qinggan decoction is mainly composed of Ligusticum chuanxiong Hort, Curcuma, Sedum rosea, and other drugs, among which Ligusticum chuanxiong Hort has



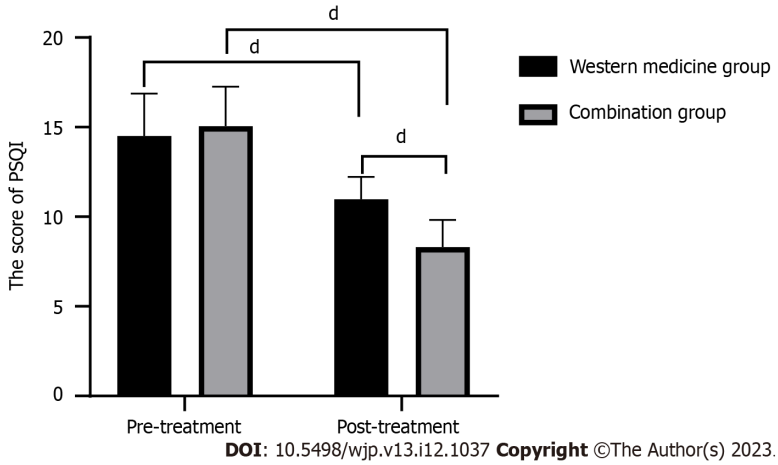
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Figure 1 Depressive state of both groups of patients at different times. HAMD: Hamilton Depression Scale.



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Figure 2 Effects of different treatment regimens on neurotransmitter levels of patients. A: Dopamine level; B: 5-hydroxytryptamine level. ^{d}P < 0.0001. 5-HT: 5-hydroxytryptamine.



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Figure 3 Effect of different treatment schemes on the sleep quality of patients. ^{d}P < 0.0001. PSQI: Pittsburgh Sleep Quality Index.

antioxidant, anticoagulant, anti-tumor, anti-inflammatory, analgesic, microcirculation improvement, anti-aging, antidepressant, anti-radiation, and other effects[21]. Curcuma can regulate neurotransmitters, regulate neuroendocrine function, protect neurons, and inhibit neuroinflammation[22]. Salidroside, an effective component of Sedum rosea, has anti-fatigue, antidepressant, immune-enhancing, and anti-tumor properties[23]. There is a synergistic effect between the active ingredients in Chuanjin Qinggan decoction which helps to improve the depressive state of patients by reducing neurological damage and providing raw materials and energy for protein and nucleic acid synthesis in the brain tissue.

In addition, this study also found that patients treated with Chuanjin Qinggan decoction combined with SSRIs experienced less pain, better treatment efficacy for herpes zoster, better sleep quality, and a lower incidence of adverse reactions compared to those treated with SSRIs alone. These results suggest that the treatment scheme of Chuanjin Qinggan decoction combined with SSRIs can not only significantly improve the depressive state of patients but also improve the treatment of herpes zoster. Chronic pain is an adverse subjective and emotional experience with attributes in multiple dimensions, including sensory recognition, emotional motivation, and cognitive evaluation. Chronic pain increases the psychological burden on patients and causes negative emotions such as disgust, anxiety, and depression. The physical and mental suffering of patients with herpes zoster and depression is severe. Psychological state has a reverse regulatory effect on physiological state, and a good psychological state can improve the effect of treatment for physiological diseases. Shahimi *et al*[24] pointed out in their study that a good psychological state can reduce the risk of falls in older adults and the risk of cardiovascular and cerebrovascular diseases. In this study, the two groups of patients received eight weeks of drug treatment, and the symptoms of herpes zoster and depression significantly improved. However, this study has certain limitations. Specifically, the sample size of this study is small and it comes from a single research center, which may result in selection bias. Further studies with larger samples or joint studies with other centers are needed to confirm the reliability of the results.

CONCLUSION

This study retrospectively analyzed the clinical data of patients with herpes zoster complicated by depression and found that different treatment schemes had different therapeutic outcomes. Patients treated with Chuanjin Qinggan decoction combined with SSRIs experienced less pain, better treatment efficacy for herpes zoster, more significant improvement in depression, a greater increase in DA and 5-HT levels, better sleep quality, and a lower incidence of adverse reactions compared to those treated with SSRIs alone. The overall curative effect of the Chuanjin Qinggan decoction combined with SSRIs was better than treatment with SSRIs alone.

ARTICLE HIGHLIGHTS

Research background

The physical and mental suffering of patients with herpes zoster combined with depression is significant. Although traditional Western medicine can alleviate the depressive symptoms in patients to a certain extent, it also causes many adverse reactions. There remains a need to identify drugs with high clinical safety that can effectively improve the depressive symptoms in patients with herpes zoster combined with depression.

Research motivation

To search for safe drugs that can effectively improve the depressive symptoms of patients with herpes zoster combined with depression, and to provide references for the formulation and modification of the treatment plan for herpes zoster combined with depression.

Research objectives

We analyzed the value of Chuanjin Qinggan decoction combined with a serotonin- selective reuptake inhibitor in the treatment of patients with herpes zoster complicated by depression.

Research methods

We retrospectively analyzed depression status, treatment effect, degree of pain, neurotransmitter levels, sleep quality, and adverse reactions in patients with herpes zoster complicated by depression who received different treatment schemes.

Research results

Compared with patients treated with selective serotonin reuptake inhibitor (SSRIs) alone, patients treated with Chuanjin Qinggan decoction combined with SSRIs showed a greater improvement in depression after treatment, and the incidence of adverse reactions was lower.

Research conclusions

The treatment scheme of the Chuanjin Qinggan decoction combined with SSRIs can improve the depressive state of patients with herpes zoster complicated by depression, and improve the effect of treatment for herpes zoster without increasing the risk of adverse reactions.

Research perspectives

In the future, the specific mechanism of Chuanjin Qinggan decoction in the treatment of herpes zoster complicated by depression should be clarified through cell or animal experiments, to provide references for further improving the therapeutic effect.

FOOTNOTES

Co-first authors: Yi-Nan Wang and Meng-Meng Shi.

Author contributions: This paper was written by Wang YN, Shi MM, and Zhang JM; Wang YN led the writing of the article; Zhang JM proofread all drafts; and Shi MM, the director of the paper, provided the first guidance; all authors contributed to revision of this paper and made constructive suggestions to ensure accurate expression of the research results. Wang YN and Shi MM contributed equally to this work and are co-first authors.

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ORIGINAL ARTICLE

Retrospective Study

Impact of an emergency department nursing intervention on continuity of care, self-care, and psychological symptoms

Song Xu, Yi-Fang Gu, Ai-Hua Dong

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Abstract

BACKGROUND

The emergency department plays a crucial role in providing acute care to patients. Nursing interventions in this setting are essential for improving the continuity of care, enhancing patients' self-care abilities, and reducing psychological symptoms.

AIM

To evaluate the effect of nursing interventions in the emergency department on these indicators in an emergency department.

METHODS

A retrospective analysis was conducted on 120 patients admitted to the emergency department between January 2022 and May 2023. The patients were divided into two groups: The control group (conventional nursing intervention) and the observation group (conventional nursing intervention + emergency department nursing intervention). The two groups were compared regarding continuity of care, self-care ability, psychological symptoms, and satisfaction with care.

RESULTS

The emergency department nursing interventions significantly improved the continuity of care, enhanced patients' self-care abilities, and reduced psychological symptoms such as anxiety and depression.

CONCLUSION

Nursing interventions in the emergency department positively impact continuity of care, self-care, and psychological symptoms. However, it is important to acknowledge the limitations of this study, including the small number of studies, variable methodological quality, and the heterogeneity of the study population. Future research should address these limitations and further explore the effects of

different types of nursing interventions in the emergency department. Additionally, efforts should be made to enhance the application and evaluation of these interventions in clinical practice.

Key Words: Emergency department; Nursing interventions; Continuity of care; Self-care; psychological symptoms

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Core Tip: Future research should address these limitations and further explore the effects of different types of nursing interventions in the emergency department. Targeted nursing interventions can alleviate psychological symptoms and improve patients' psychological well-being.

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INTRODUCTION

The emergency department is crucial for providing treatment for acute illnesses and trauma. Nursing interventions in this setting are essential for improving the continuity of care, enhancing self-care abilities, and alleviating psychological symptoms[1-5]. Emerging evidence from clinical practice indicates that these interventions positively impact the patients' overall health status[6-9]. Therefore, conducting a comprehensive study of these effects can enhance the quality of care and improve patient outcomes.

Continuity of care in the emergency department involves providing uninterrupted care throughout the patient's stay, including monitoring their condition, implementing care measures, and assessing outcomes. It has been shown that good continuity of care can effectively reduce complications and improve patient outcomes[10-15]. Self-care refers to a patient's ability to independently perform activities of daily living (ADL) and self-care while in the emergency department. Nursing interventions can improve patients' self-care abilities, reduce their reliance on healthcare professionals, and enhance their quality of life[16-23]. Psychological symptoms such as anxiety, depression, and fear are common among emergency department patients. These symptoms can negatively affect patient recovery and prolong the hospital stay [24]. Targeted nursing interventions can help alleviate psychological symptoms and improve patients' psychological well-being.

MATERIALS AND METHODS

General information

We retrospectively analyzed the data of 120 patients admitted to our hospital's emergency department between January 2022 and May 2023. The inclusion criteria were as follows: (1) Age range: Patients in the emergency department were adults aged 18 years and older; (2) primary diagnosis: patients with acute illness, trauma, or other acute medical problems requiring emergency department nursing intervention; (3) self-care: patients had some ability to care for themselves and could understand and follow instructions for nursing intervention; and (4) consent to participate: patients or their legal representatives agreed to participate in the study and signed an informed consent form. Exclusion criteria were as follows: (1) Age restriction: patients under the age of 18 years were excluded from the study; (2) critical status: severe illness or trauma requiring urgent intensive care or surgical treatment; (3) state of consciousness: patients with impaired consciousness or an unstable mental status who were unable to cooperate with the nursing intervention assessment; (4) unable to provide informed consent: patients unable to understand, express, or sign an informed consent form; and (5) previously received similar interventions: patients who had previously received an emergency department nursing intervention or a similar research intervention. The study design considered the feasibility, ethical requirements, and practicalities to ensure scientific validity and reliability.

The control group consisted of 60 patients who received conventional nursing intervention, whereas the observation group received both conventional nursing intervention and emergency department nursing intervention. The control group consisted of 30 males and 30 females, with an age range of 43-75 years (58. 41 ± 3. 17), and the length of hospital stay ranged from 7-20 d (10. 54 ± 2. 57). The observation group consisted of 29 males and 31 females, aged 44-77 years (58. 47 ± 3. 22).

The duration of hospitalization ranged from 8 to 22 d [(mean: 10. 68 ± 2. 61) d]. There were no statistically significant differences between the two groups in terms of sex, age, or duration of hospitalization (P > 0. 05).

Methodology

In the control group, routine care was provided, including maintaining a constant room temperature, regularly opening windows and doors, providing a balanced diet based on the patient's preferences, guiding the patient to change positions, and providing psychological care.

In the observation group, emergency department nursing interventions were carried out in addition to conventional nursing care: (1) Optimizing the nursing process: Improving the efficiency and quality of patient care by optimizing the nursing process and operational specifications in the emergency department. This includes the rapid assessment of patients, prioritization of treatment for critically ill patients, and prompt examinations and treatments; (2) personalized care plans: developing personalized care plans based on each patient's specific situation and diagnosis. Considering the patients' conditions, needs, and preferences, nursing interventions were tailored to their individual situations; (3) nursing education: providing relevant health education and nursing guidance to patients and their family members. This includes educating patients about the disease, treatment plans, and medication to help them better understand and cope with acute medical problems; (4) psychological support: recognizing that patients in the emergency department often experience psychological symptoms such as anxiety, fear, and stress. Nursing staff can reduce patients' psychological burdens and provide positive psychological support through active listening, reassurance, and emotional support; (5) pain management: effectively addressing and managing pain in patients with pain in the emergency department. The nursing staff assessed pain, managed medication, and provided physiotherapy to alleviate pain; (6) critical care: providing close monitoring of patients in critical conditions, including continuous monitoring of vital signs, ongoing assessment of the patient's condition, and timely intervention to ensure patient safety and stability; (7) rehabilitation and referral arrangements: Offering relevant rehabilitation advice and referral to other departments. Nursing staff can provide relevant rehabilitation advice, referral arrangements, and follow-up for patients who require rehabilitation care or need to be referred to other departments; and (8) establishing a nursing team to summarize key considerations in nursing care and improve emergency care foresight by reviewing and summarizing nursing care.

Indicators of observation

(1) The observation indicators for continuity of care include re-attendance rate into the emergency department after a visit: This indicator assesses the frequency at which patients return to the emergency department within a certain period after their initial visit; hospitalization rate: This indicator assesses whether patients require hospitalization or not. Outpatient follow-up rate: This indicator measures the proportion of patients requiring further treatment or follow-up in the outpatient clinic; and (2) Self-care ability observation indicators include assessment of ADL (0-100 points, the higher the score, the stronger the ability): This assessment evaluates the patient's ability to perform daily activities, such as eating, washing, dressing, toileting, and walking; and self-assessment scales: Patients self-report their level of self-care ability through self-assessment scales, such as the Barthel Index and Lawton Self-care Ability Scale. The observation indicators for psychological symptoms include the Symptom Self-Rating Scale (SCL-90): This scale assesses the severity of the patient's psychological symptoms.

RESULTS

The observed indicators of continuity of care were compared between the two groups of patients. Based on the data presented in Table 1, patients in the observation group demonstrated significantly lower rates of re-attendance at the emergency department after their initial visit than patients in the control group ($P < 0.05$). The ADL scores of both groups were compared before and after the intervention. Furthermore, after the intervention, the ADL scores of the patients in both groups were significantly higher than those before the intervention ($P < 0.05$), and the ADL scores of the patients in the observation group were significantly higher than those in the control group ($P < 0.05$) (Table 2). The self-care abilities of the two groups were compared before and after the intervention. The Barthel index scores of the patients in the observation group were significantly higher than those in the control group ($P < 0.05$) (Table 3). After the intervention, there was a significant decrease in the SCL-90 scores for both groups compared to those before the intervention ($P < 0.05$) (Figure 1). Additionally, the SCL-90 scores of the patients in the observation group were significantly lower than those in the control group ($P < 0.05$). The SCL-90 scores of patients in the observation group were significantly lower than those in the control group ($P < 0.05$) (Table 4).

DISCUSSION

With global economic development, the overall quality of life has improved, leading to an increase in accidents and acute diseases. Consequently, the number of patients admitted to hospitals increased annually. Patients in the emergency department commonly present severe functional disorders of the limbs, including motor, sensory, and autonomic dysfunction. These impairments significantly reduce the patient's self-care ability and can result in complications such as autonomic reflex disorders, deep vein thrombosis, and pressure sores. These complications not only cause physical and psychological harm to the patients but also impose a significant economic burden on their families.

In the emergency department, the primary treatment principle is to save the lives of patients. Additionally, efforts would be made to prevent or minimize the loss of function, reduce the occurrence of complications, and achieve the best possible recovery in the shortest time to enhance the quality of life. Although most patients are generally stable after

Table 1 The observed indicators of continuity of care between the two groups of patients are compared

Group	Re-visit rate	Hospitalization rate	Recurrence rate
Observation group (n = 60)	10 (16.67)	15 (25.00)	20 (33.33)
Control group (n = 60)	40 (66.67)	50 (83.33)	54 (90.00)
χ^2	7.281	6.310	5.431
P value	< 0.001	< 0.001	< 0.001

Table 2 Comparison of activities of daily living scores between the two groups before and after the intervention

Group	Pre-intervention	Post-intervention
Observation group (n = 60)	44.37 ± 7.32	96.74 ± 9.91[a]
Control group (n = 60)	43.28 ± 6.24	85.66 ± 8.78[a]
T value	0.124	8.732
P value	0.938	< 0.001

[a]P < 0.05 *vs* pre-intervention group.

Table 3 Comparison of self-care ability between the two groups before and after intervention (mean ± SD, points)

Group	Pre-intervention	Post-intervention	Barthel index rating scale score difference
Observation group (n = 60)	52.34 ± 6.85	78.63 ± 5.44[a]	26.28 ± 6.62
Control group (n = 60)	52.00 ± 6.32	69.72 ± 5.81[a]	17.72 ± 4.55
T value	0.209	6.330	6.032
P value	0.835	< 0.001	< 0.001

[a]P < 0.05 *vs* pre-intervention group.

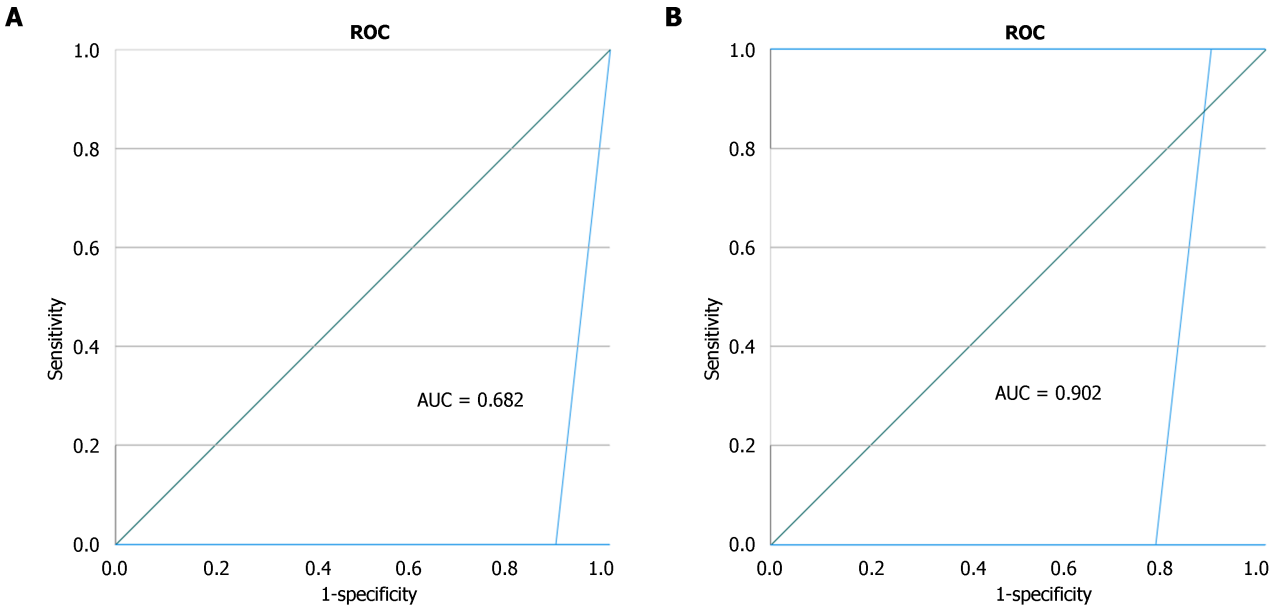
Table 4 Comparison of Symptom Self-Rating Scale scores before and after the intervention in the two groups (mean ± SD, points)

Group	Pre-intervention	Post-intervention	Poor SCL-90 score
Observation group (n = 60)	234.69 ± 25.35	162.44 ± 15.48[a]	72.25 ± 20.00
Control group (n = 60)	235.50 ± 26.29	187.41 ± 16.53[a]	48.09 ± 17.45
T value	-0.126	6.236	5.149
P value	0.900	< 0.001	< 0.001

[a]P < 0.05 *vs* pre-intervention group. SCL-90: Symptom Self-Rating Scale.

treatment, they still require long-term care. Studies have confirmed that emergency department nursing, in addition to routine nursing, can improve patients' motor functions, reduce the incidence of complications, and improve their quality of life.

The impact of emergency department nursing interventions on continuity of care, self-care, and psychological symptoms is an area of considerable research interest[25]. The literature review presented here highlights the fact that numerous studies have explored the impact of various emergency department nursing interventions on these aspects. In the cardiovascular field, interventions, such as home environment interventions and telephone support, have been found to enhance patient self-care and quality of life. These interventions empower patients to manage their condition better and provide them with support, thereby improving their understanding and ability to cope with their illness. Additionally, studies have focused on emergency department nursing interventions for critically ill patients and those with heart failure, indicating the potential of these interventions in improving patients' self-care and psychological symptoms. In addition, for patients with heart failure and severe infections, the implementation of early fluid resuscitation in the emergency department has shown potential benefits in improving self-care and reducing psycho-



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Figure 1 Impact of emergency department nursing intervention on continuity of care, self-care and psychological symptoms. A: Before intervention; B: After intervention. ROC: Receiver operating characteristic; AUC: Area under the curve.

logical symptoms. These interventions can improve the physiological status of patients and facilitate their recovery and rehabilitation. Taken together, emergency department nursing interventions have a positive impact on the continuity of care, self-care, and psychological symptoms.

CONCLUSION

Emergency department care can help patients improve their caregiving capacity, reduce psychological symptoms, and improve their quality of life through individualized nursing interventions, self-management support, and early interventions. However, further research is needed to explore the impact of different types of emergency department nursing interventions on diverse populations and conditions to provide more accurate guidance and best practices. This study has limitations in terms of sample size, diversity of interventions, and time constraints. Additionally, the complexity of the emergency department settings may introduce other uncontrolled interventional factors.

ARTICLE HIGHLIGHTS

Research background

The emergency department plays a crucial role in providing acute care to patients, and nursing interventions in this setting are essential for improving continuity of care, enhancing patients' self-care abilities, and reducing psychological symptoms.

Research motivation

To evaluate the impact of nursing interventions in the emergency department on these indicators in an emergency department.

Research objectives

This study examined various indicators of continuity of care, self-care, and psychological symptoms.

Research methods

A retrospective analysis was conducted on 120 patients admitted to the emergency department between January 2022 and May 2023. The patients were divided into two groups: The control group (conventional nursing intervention) and the observation group, which received both conventional nursing and emergency department nursing interventions. Patients in both groups were compared in terms of continuity of care, self-care ability, psychological symptoms, and satisfaction with care.

Research results

The emergency department nursing interventions significantly positively impacted various aspects. Specifically, these interventions improved the continuity of care, enhanced patients' self-care abilities, and reduced psychological symptoms such as anxiety and depression.

Research conclusions

Additionally, the complexity of the emergency department settings introduces the possibility that other uncontrolled intervention factors may have an impact.

Research perspectives

Emergency department nursing interventions have the potential to improve patients' self-care and psychological symptoms, suggesting their effectiveness. Furthermore, the implementation of early fluid resuscitation in the emergency department has shown potential benefits for patients with heart failure and severe infections, leading to improved self-care and reduced psychological symptoms. These interventions can improve the patient's physiological status and facilitate recovery and rehabilitation.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Effect of cognitive behavior therapy training and psychological nursing on the midwifery process in the delivery room

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Abstract

BACKGROUND

The severe physical and psychological impact of pain on the physical and mental health of women during labor leads to increased risks and complications during childbirth, presenting a major public health concern. Some studies have shown that cognitive behavioral therapy (CBT) has a positive effect on maternal psychology during delivery, reducing stress and shortening labor time. Thus, CBT training for mothers and delivery room staff may be beneficial in minimizing complications and adverse effects during natural birth.

AIM

To investigate the clinical effects of CBT training and psychological care during delivery, and their therapeutic effects on women in labor.

METHODS

This study used a retrospective analysis and included 140 mothers admitted to the maternity ward between January 2021 and January 2023. The study subjects were randomized into two groups: control (n = 70) and observation (n = 70). Routine care, CBT training, and psychological care were provided to mothers in both groups. Psychological status scores, delivery time, and satisfaction with care pre- and post-delivery were compared, and the incidence of complications after receiving care was analyzed between the two groups.

RESULTS

Although the psychological state of both groups improved significantly in the late stages of labor, the psychological state scores of the mothers in the observation group were significantly lower than those of the mothers in the control group (P < 0.05). The duration of labor and incidence of complications in the observation group were significantly lower than those in the control group (P < 0.05). The mothers in the observation group were significantly more satisfied with nursing care during the course of labor than those in the control group (P < 0.05).

CONCLUSION
CBT training and psychological care for mothers in the midwifery process can effectively improve anxiety and depression, shorten labor duration, reduce postnatal complications, and improve nursing satisfaction and nurse-patient relationships. Its clinical application is effective and has popularization value, providing a new way to protect maternal mental health.

Key Words: Cognitive behavior therapy; Cognitive behavior therapy training; Psychological care; Childbirth; Mental health

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Core Tip: The application of cognitive behavior therapy training and psychological care in the delivery process can effectively improve the psychological condition of mothers, shorten labor duration, reduce the incidence of complications, and improve nurse-patient relationships and nursing satisfaction. Compared to either approach alone, the effect of the combined intervention was more significant.

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INTRODUCTION

During labor, the resulting pain causes strong psychological stimulation in women, often leading to accidents due to excessive mental stress[1,2]. Psychological factors have a strong influence on childbirth and are considered to be the fourth stage after the dilation, expulsion, and placental stages[3]. Mild anxiety is a normal psychological stress that can be accompanied by moderate activation of the sympathetic nervous system, improving the body's ability to adapt to the environment; however, the following question arises: How can excessive anxiety or stress lead to physiological alterations during labor[4,5]? First, excessive anxiety leads to a decrease in norepinephrine production, resulting in weak uterine contractions, which can, in turn, lead to obstructed labor and is a possible factor in increasing the risk of postpartum hemorrhaging[6]. Second, stress and anxiety may exacerbate contraction pain by causing a relative decrease in the mother's pain threshold. Severe pain and poor maternal mood also promote catechol secretion in the body, causing uncoordinated uterine contractions, thus impeding the ongoing labor process and increasing the chances of obstructed childbirth as well as decreasing uterine blood flow, which can also cause fetal hypoxia[7,8].

Previous surveys have shown that more than 90% of pregnant women experience labor pain, physiological changes during pregnancy, and anxiety prior to delivery. Mothers who are fearful of a natural birth are more likely to develop other psychological conditions after birth, such as postnatal depression, than those who are not[9]. Incidences of obsessive-compulsive disorder and generalized anxiety disorder are also much higher in postpartum women than in those who have not given birth[10]. Especially in China, since the implementation of the two-child policy, the incidence of postpartum depression has increased significantly. Statistics show that the annual incidence of postpartum depression in China is 5.36%-11.09%[11]. However, numerous studies have demonstrated that timely and effective psychological interventions during labor can significantly reduce maternal fear and tension and increase the rate of successful delivery. Natural childbirth, led by midwives, reduces the risks of pregnancy[12]. Midwives are primarily responsible for providing health education to mothers and their families during labor and delivery, increasing mothers' confidence in a smooth delivery through constant encouragement and reassurance, and by reducing fear, pain, and anxiety[13]. A previous study found that cognitive behavioral therapy (CBT) training before childbirth can help reduce anxiety and tension, decrease the duration of childbirth, and improve mothers' quality of life[14]. Psychological care, however, is aimed at changing the mother's psychological condition during childbirth and is targeted to help improve her mood and reduce fear of a natural birth, thus reducing the incidence of adverse birth events. However, to the best of our knowledge, only a few studies have combined CBT training and psychological care to provide childbirth assistance.

This study used a retrospective approach to investigate the clinical effects of CBT training and psychological care for mothers during assisted delivery and provide new insights into reducing labor complications as well as safeguarding mothers' physical and mental health.

MATERIALS AND METHODS

Study design, setting, and participants

This retrospective study included 140 women who had previously received CBT training and psychological care from midwives as study subjects in the hospital. Subjects who received combined care were included in the observation group

(n = 70), and those who received either psychological care or CBT training alone were included in the control group (n = 70). The psychological status scores, delivery time, and satisfaction with nursing care were compared pre- and post-delivery and the rate of complications after receiving nursing care were analyzed in both groups. The study subjects met the following criteria: (1) Single full-term vaginal births; (2) complete, true, and valid clinical data; (3) signed informed consent form subjects and their families after being informed of the study purpose and content; (4) no history of psychiatric or psychological disorders, or language or cognitive impairment; and (5) no serious comorbidities. The attending physicians met the guidelines for vaginal delivery.

The control group was selected from among the subjects who received either CBT training or psychological care only during the midwifery process, whereas the observation group received both. Except for the noted cognitive and/or psychological interventions, the same care model was applied to both groups.

Regarding routine nursing care, the nursing staff conducted consistent routine nursing care for all mothers, including the following: (1) Providing health education to the mothers and their families (*i.e.*, informing them of the relevant precautions and popular knowledge related to childbirth); (2) assisting the mother in the correct position during labor, instructing her to breathe and exert herself reasonably, and answering her questions about the childbirth process; and (3) enhancing the monitoring of maternal vital signs during labor, instructing family members and mothers to implement postnatal care, and instructing mothers to pay attention to rest, scientific diet, and good hygiene.

Regarding CBT training, when a mother is admitted to the hospital for delivery, the nursing staff learn about her cognitive and comprehension abilities. This, in turn, allows for the adoption of various informational approaches, such as lectures, videos, props and models, and health education manuals to help her grasp the delivery-related knowledge, making her comprehensively aware of the advantages and disadvantages of vaginal delivery and cesarean section, and helping enhance her confidence in delivery. The following is an overview of the instructions: (1) During the first stage of labor, close attention is paid to the mother's labor contractions, instructing her to conduct breathing training and leading her to a free position where she chooses to stand, squat, sit, or lay down while waiting for delivery to provide favorable conditions for the fetus's head to descend, rotate, and be delivered; (2) During the second stage of labor, when the vagina is fully dilated, the recorded video is played back to correctly guide exertion, while changes in the vital signs are closely observed. If abnormalities are found, the doctor is promptly informed and helps in strictly implementing an aseptic operation to avoid infection during labor and the contraction period, to guide the food and water, and to maintain good stamina to lead the head of the fetus to the crown; and (3) During the third stage of labor, when the placenta is delivered, the presence of soft birth canal laceration is checked and, if present, timely suture treatment is provided. At the end of childbirth, the mother is closely monitored, especially for any instances of vaginal bleeding, and guidance for perineal cleansing, supplemented by abdominal massage, is provided to promote contractions and reduce bleeding. If a vaginal delivery is not possible, the mode of delivery should be changed according to the actual situation to avoid irreversible and serious consequences.

Regarding psychological care, prior to delivery, women often experience negative psychological emotions, such as anxiety and depression, due to labor pain and fear for fetal safety. Nursing staff must comprehensively assess changes in their psychological emotions, determine the influencing factors, and provide targeted guidance and encouragement, allowing mothers to maintain a normal or positive state of mind prior to delivery. During labor, an entire process of encouragement and guidance for women is implemented to alleviate such adverse emotions and emotional stress. Post-delivery, the mother is informed promptly of the successful completion of the delivery process to eliminate her worries. Simultaneously, the mother and baby are placed in the same room as soon as possible, and breastfeeding is started as early as possible to help with breast milk secretion and support the mother's adaptation to motherhood.

Measurement of variables

The psychological state score, delivery time, and satisfaction with nursing care before and after delivery in both patient groups were compared, and rates of complications after receiving nursing care were analyzed. The psychological state score is comprised of the self-rating anxiety scale (SAS) and self-rating depression scale (SDS); the lower the score, the better the psychological state of the patient. The duration of childbirth in both groups included the average duration of the first, second, and third stages. Incidence of postpartum complications in the two groups included weak contractions, postpartum hemorrhage, and postpartum depression. Satisfaction with nursing care was assessed using a self-developed scale with four dimensions: basic nursing care, nursing methods, nursing intervention, and nursing care attitude. The scores showed a positive correlation with satisfaction with nursing care; the higher the scores, the higher the satisfaction with nursing care.

Statistical analysis

Data in this study were statistically analyzed using SPSS 26.0. Continuous data conformed to the normal distribution described by means and percentages, median range (interquartile range) was used to describe continuous variables with skewed distributions, and categorical variables were summarized as numbers and percentages (%). Differences between two groups of quantitative data were analyzed using t-tests, and multiple groups of data were analyzed using chi-square tests. Analyses were set to a significance level of $\alpha = 0.05$, and differences were specified as statistically significant at $P < 0.05$.

RESULTS

Baseline data and pathological characteristics

A total of 140 subjects were included in the study. The baseline data of the study subjects were collected for comparison, which showed no statistically significant difference between age, weight, domicile, number of births, or gestational weeks between the two study groups ($P > 0.05$), and the data of the two groups were comparable. The mean age of the study subjects in the observation group was 27.23 ± 1.46 years, the mean weight was 72.91 ± 5.44 kg, the gestational period was 39.41 ± 1.22 wk, and the number of births was 1.23±0.30. In the control group, the mean age of the study subjects was 27.25 ± 1.25 years, the mean weight was 72.91 ± 5.44 kg, the gestational period was 39.25 ± 1.30 wk, and the number of births was 1.18 ± 0.21. The characteristics of the study subjects are presented in Table 1.

Mental status scores before and after delivery in both groups

The psychological state scores of the mothers before and after delivery were assessed in both groups, and the results showed no statistically significant differences from those of the mothers before delivery. After childbirth, the SAS and SDS scores of the observation group were significantly higher than those of the control group ($P < 0.05$). The mental status results are presented in Table 2.

Comparative analysis of delivery time in the two groups

Labor duration was recorded in both groups, showing differences from the first stage of childbirth onwards, with a significant decrease in childbirth time in the observation group compared with the control group ($P < 0.05$). The findings show that the combined intervention was effective in shortening childbirth time (Table 3).

Incidence of complications in both groups

Statistics on the incidence of complications during delivery in both groups showed that in the observation group, two (2.86%) women had postpartum depression, three (4.29%) had postpartum hemorrhage, three (4.29%) had weak contractions, and the total incidence of complications was eight (11.43%). In the control group, 10 (14.29%) mothers developed postpartum depression, seven (10.0%) had postpartum hemorrhage, and 11 (15.71%) developed contraction weakness; the overall complication rate was 28 (40.0%). There was a statistically significant difference in the incidences of complications between the two groups ($P < 0.05$). The complications results are presented in Table 4.

Comparative analysis of nursing satisfaction

Both groups of mothers were asked to rate their satisfaction with nursing care during childbirth. Subjects rated their satisfaction in four dimensions: basic nursing care, nursing methods, nursing intervention, and nursing care attitude. The results show that nursing care satisfaction in the observation group was higher than that in the control, and the difference was statistically significant ($P < 0.05$). The results are presented in Table 5.

DISCUSSION

This study compared the clinical effects of combined CBT training and psychological care for mothers during the process of assisted delivery with those of a single psychological intervention. The results demonstrated that, although the psychological state of mothers in both groups improved significantly in the later stages of labor, the psychological state scores in the observation group were significantly lower than those in the control group. The duration of labor and incidence of complications in the observation group were significantly lower than those in the control, and the satisfaction of mothers with care during the process of labor in the observation group was significantly higher than that in the control. In addition, labor duration and complication rates in the observation group were significantly lower than those in the control group, and the satisfaction rate in the observation group was significantly higher than that in the control group.

Childbirth is an important physiological process that mothers must undergo[15]. During childbirth, many mothers experience greater stress and emotional fluctuations accompanied by anxiety and fear. This leads to sympathetic nerve excitation, resulting in an increased small rate, respiratory frequency, and insufficient gas exchange in the lungs. These changes can cause uterine hypoxia and slow expansion of the uterine opening, causing difficulty in childbirth, prolonging labor duration, and increasing the rate of obstructed labor, as well as the risk of postpartum complications. Previous studies have demonstrated that both CBT training and psychological care can significantly reduce maternal anxiety and fear during labor and improve postnatal quality of life[16,17]. That is, the use of CBT training is effective in reducing maternal anxiety during the postpartum period. It has also been shows to reduce the complications of postpartum stress and depression, with follow-up showing improvements in family well-being and parent-child relationships during the postpartum period[18,19]. The results of this study show that compared to either CBT training or psychological care alone, a combination of the two is more effective in improving the psychological state of mothers after delivery and in reducing the incidence of postpartum depression.

Labor duration has been associated with childbirth complications in previous studies, and maternal anxiety during labor significantly affects its duration[20,21]. The present study showed that CBT training and psychological care during assisted labor were effective in reducing labor duration. The study also found a relative reduction in the incidence of post-delivery complications in the observation group. Moreover, increased satisfaction with care was effective in improving the relationship between mothers and caregivers, leading to mothers' increased trust in midwives during

Table 1 General information about the study population

		Observation group (*n* = 70)	Control group *n* = 70)	*t*/χ^2	*P* value
Age (yr)		27.23 ± 1.46	27.25 ± 1.25	0.982	0.902
Weight (kg)		72.91 ± 5.44	72.91 ± 5.44	1.973	0.981
Domicile	Urban	56	55		0.214
	Rural	14	15		
Weeks of pregnancy (wk)		39.41 ± 1.22	39.25 ± 1.30	0.712	0.131
No. of deliveries		1.23 ± 0.30	1.18 ± 0.21	0.561	0.056

Table 2 Maternal psychological state score before and after delivery

	Before childbirth		After childbirth	
	SAS	SDS	SAS	SDS
Observation group	57.25 ± 1.68	57.57 ± 2.55	51.35 ± 1.23	50.41 ± 1.33
Control group	57.39 ± 1.87	57.49 ± 2.61	48.78 ± 1.15	47.88 ± 1.21
t	1.241	0.987	7.812	6.902
P value	0.521	0.712	< 0.001	< 0.001

SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

Table 3 Comparative analysis of two groups of maternal labor time

	The first stage of labor (h)	The second stage of labor (min)	The third stage of labor (min)
Control group	8.26 ± 1.76	45.32 ± 7.25	9.29 ± 1.37
Observation group	6.15 ± 1.21	33.19 ± 5.35	6.33 ± 0.91
t	7.193	14.210	11.021
P value	< 0.001	< 0.001	< 0.001

Table 4 Comparative analysis of the incidence of post-delivery complications between both groups

	Postpartum depression	Postpartum hemorrhage	Weak contractions	Total incidence of complications
Observation group, *n* (%)	2 (2.86)	3 (4.29)	3 (4.29)	8 (11.43)
Control group, *n* (%)	10 (14.29)	7 (10.0)	11 (15.71)	28 (40.0)
χ^2				23.914
P value				< 0.001

Table 5 Comparative analysis of maternal nursing satisfaction between both groups

	Basic nursing care	Nursing methods	Nursing intervention	Nursing care attitude
Observation group	94.24 ± 2.81	96.91 ± 2.92	94.45 ± 1.91	97.89 ± 3.14
Control group	90.89 ± 1.12	91.21 ± 1.14	90.14 ± 0.94	92.94 ± 1.58
t	7.193	14.210	11.021	8.931
P value	< 0.001	< 0.001	< 0.001	< 0.001

labor[22].

The strength of this study is in its combined use of CBT training and psychological care, evaluated in terms of psychological status scores, labor duration, postpartum complications, and satisfaction with care. However, due to the retrospective nature of the study, the extent of support for the exact efficacy and safety of the intervention was not as high as that of a prospective study. Nonetheless, we obtained complete clinical data and avoided errors caused by incomplete data.

CONCLUSION

In conclusion, CBT training and psychological care for mothers in the midwifery process can effectively improve maternal anxiety and depression, shorten labor duration, reduce postnatal complications, and improve nursing satisfaction and nurse-patient relationships. Its clinical application is effective and has popularization value, offering a new way to protect maternal mental health.

ARTICLE HIGHLIGHTS

Research background

The severe physical and psychological impact of pain on the physical and mental health of women during childbirth, leads to increased risks and complications, presenting a major public health issue.

Research motivation

During childbirth, labor pain causes strong psychological stimulation in women, which often leads to accidents due to excessive mental stress.

Research objectives

To provide new insights into reducing accidents during childbirth and safeguarding mothers' physical and mental health.

Research methods

This study used a retrospective analysis and included 140 mothers admitted to the maternity ward between January 2021 and January 2023. The two groups were randomized: Routine care, cognitive behavior therapy (CBT) training, and psychological care were, respectively, provided to mothers in the control (n = 70) and the observation (n = 70) groups.

Research results

The results showed that although the psychological state of mothers in both groups improved significantly in the late stage of labor, that of the mothers in the observation group was significantly lower than that of mothers in the control group. The labor duration and incidence of complications in the observation group were significantly lower than those in the control group, and the satisfaction of mothers with care during the process of labor in the observation group was significantly higher than that in the control group. In addition, labor duration and complication rates in the observation group were significantly lower than those in the control group, and the satisfaction rate in the observation group was significantly higher than that in the control group.

Research conclusions

CBT training and psychological care for mothers in the midwifery process can effectively improve maternal anxiety and depression, shorten labor duration, reduce postnatal complications, and improve nursing satisfaction and nurse-patient relationships. Its clinical application is effective and has popularization value, providing a new way to protect the mental health of mothers.

Research perspectives

CBT training and psychological care were administered during the delivery process, and the clinical effects were assessed by evaluating the psychological state scores of the mothers after delivery, observing labor duration, incidence of post-delivery complications, and satisfaction with nursing care.

FOOTNOTES

Author contributions: Shi Q and Gu LY contributed equally to this work; Shi Q, Wang J, Zhao D and Gu LY designed the research study; Shi Q, Wang J, Zhao D and Gu LY performed the research; Shi Q and Gu LY contributed new reagents and analytic tools; Shi Q and Gu LY analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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Informed consent statement: All research participants signed informed consent forms before the study.

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ORIGINAL ARTICLE

Retrospective Study

Meteorological factors, ambient air pollution, and daily hospital admissions for depressive disorder in Harbin: A time-series study

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Abstract

BACKGROUND

The literature has discussed the relationship between environmental factors and depressive disorders; however, the results are inconsistent in different studies and regions, as are the interaction effects between environmental factors. We hypothesized that meteorological factors and ambient air pollution individually affect and interact to affect depressive disorder morbidity.

AIM

To investigate the effects of meteorological factors and air pollution on depressive disorders, including their lagged effects and interactions.

METHODS

The samples were obtained from a class 3 hospital in Harbin, China. Daily hospital admission data for depressive disorders from January 1, 2015 to December 31, 2022 were obtained. Meteorological and air pollution data were also collected during the same period. Generalized additive models with quasi-Poisson regression were used for time-series modeling to measure the non-linear and delayed effects of environmental factors. We further incorporated each pair of environ-

mental factors into a bivariate response surface model to examine the interaction effects on hospital admissions for depressive disorders.

RESULTS

Data for 2922 d were included in the study, with no missing values. The total number of depressive admissions was 83905. Medium to high correlations existed between environmental factors. Air temperature (AT) and wind speed (WS) significantly affected the number of admissions for depression. An extremely low temperature (-29.0 ℃) at lag 0 caused a 53% [relative risk (RR)= 1.53, 95% confidence interval (CI): 1.23-1.89] increase in daily hospital admissions relative to the median temperature. Extremely low WSs (0.4 m/s) at lag 7 increased the number of admissions by 58% (RR = 1.58, 95%CI: 1.07-2.31). In contrast, atmospheric pressure and relative humidity had smaller effects. Among the six air pollutants considered in the time-series model, nitrogen dioxide (NO_2) was the only pollutant that showed significant effects over non-cumulative, cumulative, immediate, and lagged conditions. The cumulative effect of NO_2 at lag 7 was 0.47% (RR = 1.0047, 95%CI: 1.0024-1.0071). Interaction effects were found between AT and the five air pollutants, atmospheric temperature and the four air pollutants, WS and sulfur dioxide.

CONCLUSION

Meteorological factors and the air pollutant NO_2 affect daily hospital admissions for depressive disorders, and interactions exist between meteorological factors and ambient air pollution.

Key Words: Mental health; Depressive disorder; Hospital admissions; Meteorological factors; Air pollution; Time-series

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Core Tip: This retrospective study assessed the influence of environmental factors on depressive disorders. Daily hospital admissions for depressive disorders at a hospital in Harbin, China from 2015 to 2022 were obtained. Four meteorological factors and six air pollutants were considered predictors in the time-series models. Air temperature, atmospheric pressure, wind speed, relative humidity, and nitrogen dioxide have effects on daily hospital admissions for depressive disorders, and interactions exist between meteorological factors and ambient air pollution.

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INTRODUCTION

Depressive disorder (also known as depression) is a common mental disorder that involves depressed mood and loss of pleasure or interest in activities for long periods of time[1]. Approximately 280 million people (3.8%) worldwide experience depression[2]. Depressive disorder is a complex phenomenon that represents the interplay between social, psychological, and biological mechanisms[1]. The crucial biochemical mechanism underlying depression lies in the disruption of synaptic chemical transmission, which leads to a functional deficiency in the brain's monoaminergic transmitters including norepinephrine, serotonin (5-hydroxytryptamine), and/or dopamine[3]. These mechanisms have become targets of antidepressant action; for example, selective serotonin reuptake inhibitors such as fluoxetine are typical antidepressant medications[1] used for regulating serotonergic transmission.

In the last couple of years, accumulated evidence suggests that depressive disorder is also affected by environmental factors[4], including meteorological factors[5-8], ambient air pollution[9-13], light exposure[14-16], and access to green space[17,18]. An increase in temperature has been found to exacerbate psychiatric disease hospitalizations[19] in Greece, deteriorate mental well-being, and increase depressive language and suicide rates[20] in North America. Exposure to fine particles ($PM_{2.5}$), inhalable particles (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO) was positively associated with depression, and the risk of depression increased with exposure to high levels of these pollutants[21]. Sunlight intensity may also be associated with depressive symptoms[22]. People reporting inadequate natural light in their dwellings were more likely to report depression[15]. This strongly suggests that environmental factors play a role in altering serotonin levels, leading to depression. Corresponding therapies, such as bright-light therapy, have been developed and used, and have evolved into effective treatments that act on serotonin and other monoaminergic pathways[16].

While the literature has discussed the relationship between environmental factors and depressive disorders, the interactions between different environmental factors have rarely been considered. Moreover, the results of different studies have been inconsistent. This study aimed to investigate the effects of environmental factors on depressive disorders. We obtained environmental data containing four meteorological factors and six air pollutants and modeled the

interactions between these environmental factors simultaneously to gather more precise evidence and obtain a regional supplement for this research field.

MATERIALS AND METHODS

Study design

To measure the precise effects of and the interaction between meteorological factors and air pollution on depressive disorders, we obtained as our sample daily hospital admission data for depressive disorders at a class 3 hospital in Harbin, China from January 1, 2015 to December 31, 2022. Data on the meteorological factors and air pollution for each day of admission were also collected to construct a predictive model.

Data collection

Data from 2922 d were obtained from the information management system developed and used by the hospital. Patient information included the visit time and diagnosis. Individual identifiers were excluded. Patients with permanent residence in Harbin were selected, and those with other mental disorders were excluded. Daily depressive disorder admission data equaled the sum of depressive outpatient and hospitalization data. The diagnosis of depressive disorder (coded as F32-F33 ICD-10 diagnoses) refers to GB/T 14396-2016", classification and Code of Diseases"[23].

Meteorological data for the same period from 2015 to 2022 for Harbin, China, were collected from the China meteorological data service centre[24], including daily mean air temperature (AT), daily mean atmospheric pressure (AP), wind speed (WS), and relative humidity (RH).

Ambient air pollution data included six international standard air pollutants that have been extensively investigated previously[12]: $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and ozone (O_3, usually measured at maximum 8-h average concentrations). The pollutant data were collected from the China Air Quality Online Monitoring and Analysis platform[25]. For all ambient air pollutants, we averaged all valid monitoring measurements each day to obtain their daily mean concentrations, in line with previous studies[12,26].

To conduct a time-series analysis, information on time-related variables was collected for modeling, such as the day of admission and public holidays. A sequence of calendar times was generated to indicate the time trends.

Statistical analysis

All data were inspected and preprocessed using Microsoft excel and IBM SPSS 25.0. No missing values or outliers were identified. Descriptive analysis, correlation calculations, time-series modeling, and plotting were conducted using R version 4.2.3. The mean value; SD; and minimum, maximum, median, and quartile (P_{25} and P_{75}) were used to describe the data. The correlation coefficients between variables were calculated using Spearman's correlation analysis with the R package psych. We conducted a time-series analysis using the R packages dlnm[27], mgcv[28], rsm[29], and splines, modeling the effects of and interactions between various environmental factors. The R package ggplot2[30] was used to visualize the results. All statistical tests were two-tailed probability tests, $\alpha = 0.05$. Statistical results with $P < 0.05$, such as associations and differences, were considered statistically significant.

We used generalized additive models with quasi-Poisson regression to estimate the meteorological effects of each factor. The covariates in the models included a natural cubic spline of calendar time with 14 degrees of freedom, which modeled time trends in hospital admissions for depressive disorders, and two indicator variables for the day of the week and public holidays, accounting for potential variations in hospital admissions over weekdays, weekends, and holidays. Natural cubic splines of the daily AT, AP, WS, and RH with three degrees of freedom were included as predictors. To assess the potential lagged effects of meteorological factors, we included lags of up to seven days in the model for non-cumulative effects, similar to the methodology of a previously published study[31]. The choice of calendar time *df* was determined by calculating the minimum sum of the absolute values of the partial autocorrelation function based on the residuals of the underlying model, consistent with the residual independence principle[31]. Choices of meteorological factors *df*s have been recommended by papers on time-series analyses[32] and have been adopted by most studies. The time-series analysis model for a single meteorological factor is as follows:

$$Y_t \sim quasiPoisson\,(\mu_t)$$

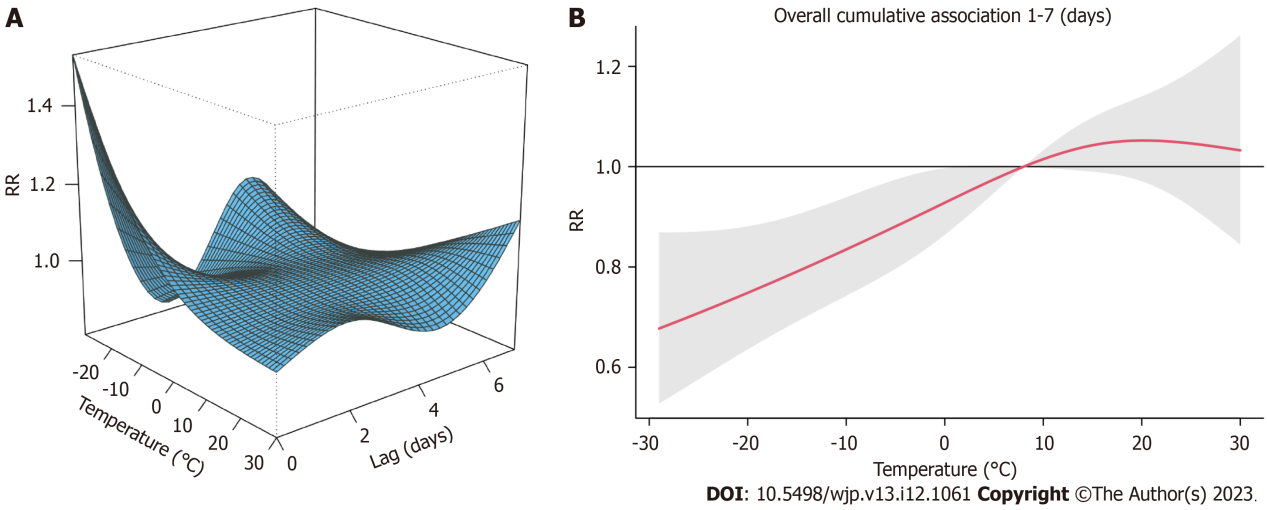
$$log\,E\,([Y_t]) = \alpha + ns_t\,(calendar\ time, df = 14) + DOW_t + holiday_t + \beta_{it} \times ns_{it}\,(meteological\ factor, df = 3)$$

Where E (Y_t) denotes the expected number of depressive disorder admissions on day t; α is the intercept; ns represents the natural cubic spline function; and β_{it} is the exposure coefficients of meteorological factors and their lagged effects. We included the immediate and lagged effects of each air pollutant in the model and used meteorological factors as covariates. The time-series analysis model for a single air pollutant is as follows:

$$Y_t \sim quasiPoisson\,(\mu_t)$$

$$\log E\,([Y_t]) = \alpha + ns_t\,(calendar\ time, df = 14) + DOW_t + holiday_t + \beta_{it} \times ns_{it}\,(meteological\ factor, df = 3) + \beta_{jt} \times (air\ pollutant)_{jt}$$

Where (air pollutant) represents lags of 0 to 7 for cumulative and non-cumulative exposures. Finally, we incorporated each meteorological factor and air pollutant into a bivariate response surface model to inspect the interaction effects of each pair of meteorological factors and air pollutants on hospital admissions for depressive disorders. The model for interaction effects is as follows:



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Figure 1 Effects of air temperature on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along air temperature and lags, with reference to the median temperature of 7.8 ℃; B: Overall RR of lags 1-7 by air temperature, with reference at 7.8 ℃. RR: Relative risk.

$$Y_t \sim quasiPoisson\,(\mu_t)$$

$$\log E\,([Y_t]) = \alpha + ns_t\,(calendar\ time, df = 14) + DOW_t + holiday_t + t_e\,(meteological\ factor_t, air\ pollutant_{t-i})$$

Where t_e is the interaction effect of meteorological factors and air pollutants (on the day with the strongest lag effect) on daily hospital admissions for depressive disorders. Results are expressed as relative percentage change (%) and estimated 95% confidence intervals (CIs) at hospital admissions for depressive disorders of certain meteorological factor levels or per unit increment of air pollutants.

RESULTS

Descriptive statistics and correlation

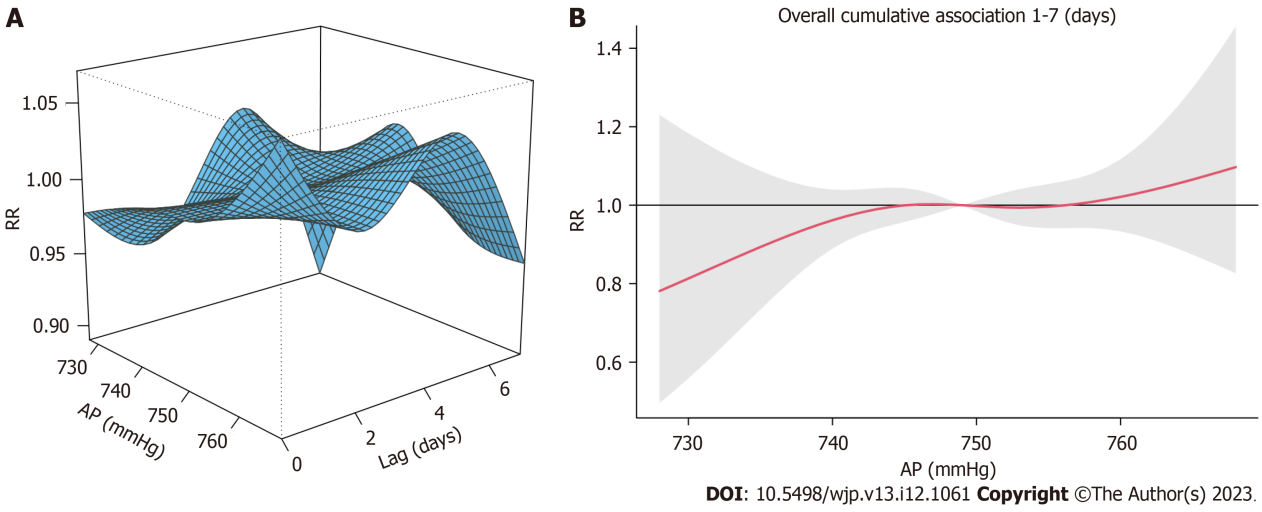
The general features of all the variables are summarized in Table 1. The total number of hospital admissions for depressive disorders from January 1, 2015 to December 31, 2022 included in the study was 83905, with a daily average admissions of 28.7. During the studied period, the daily average AT in Harbin was 5.4 ℃, and the daily average AP was 749.3 mmHg. The average WS was 2.9 m/s. The mean RH was 66.2%. The climate in Harbin is cold but mild, which means that it is not excessively windy or dry most times of the year, and the AP remains slightly lower than the standard. The daily average concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3_8h (the maximum 8-h average concentration of ozone) were 47.2 μg/m^3, 71.3 μg/m^3, 22.0 μg/m^3, 0.9 mg/m^3, 36.7 μg/m^3, and 75.8 μg/m^3, respectively. There is relatively high variability in air pollution, although the concentration levels are usually low according to the quartiles.

The correlation coefficients between the meteorological factors and air pollutants are shown in Table 2. All Spearman's correlation coefficients were statistically significant, except for the correlation between RH and CO. There was a moderate correlation among AT, AP, and air pollutants. Relatively high correlations among the air pollutants (except for O_3) were found.

Time-series analysis modeling

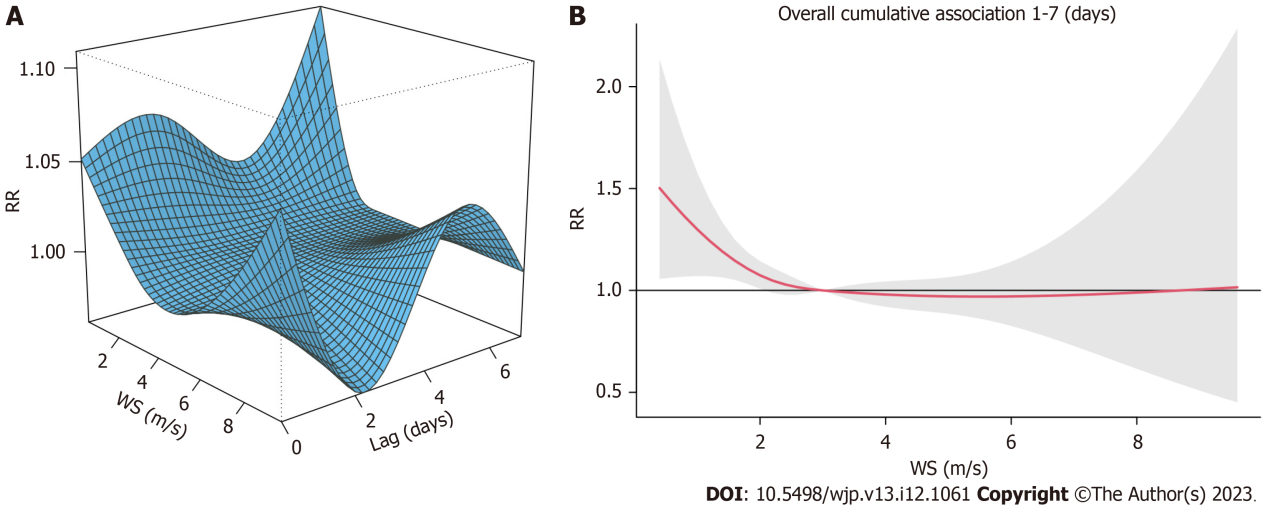
In the single meteorological factor model for AT, AP, WS, and RH, we reported relative risks (RRs) with 95%CIs of the depressive disorder admissions for each level of the meteorological factor. The overall relationships between each meteorological factor and hospital admissions for depressive disorders are summarized in Figures 1-4. As shown in Figure 1A, there was a sharp effect of extremely low temperature, although, in Figure 1B, the overall low temperature had no positive effect on RR. Figure 2 shows the mild effect of AP on RR, which is close to zero. Figure 3 shows a larger effect of low WS and a smaller effect of high WS. As shown in Figure 4, both moderate and high RH appeared to have relatively small effects.

To provide more certainty and precision in the estimates, we further investigated the effect of each meteorological factor by calculating and plotting the RRs by these factors at lags 0-7, as shown in Figures 5-8. The results for AT showed significant increases at lags 0-2 and 5-6. Figure 5 shows that an extremely low temperature (-29.0 ℃) at lag 0 increased daily hospital admissions for depressive disorders by 1.53 times (95%CI: 1.23-1.89) relative to median temperature (7.8 ℃), which was the largest effect of AT. As shown in Figure 6, the effect of AP was significant only at lags 5 and 6. A moderately high AP (762 mmHg) at lag 5 increased the number of admissions by 1.13 times (95%CI: 1.00-1.27) relative to the median AP (748.9 mmHg). Figure 7 shows that WS had a significant effect at lags 2-7. The largest effect was at lag 7, where an extremely low WS (0.4 m/s) increased the number of admissions by 1.58 times (95%CI: 1.07-2.31) relative to the median WS (2.6 m/s). Relatively high RHs at lags 4-7 had statistically significant effects, and the largest effect of RH



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Figure 2 Effects of atmospheric pressure on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along atmospheric pressure (AP) and lags, with reference to the median AP of 748.9 mmHg; B: Overall RR of lags 1-7 by atmospheric pressure, with reference at 748.9 mmHg. RR: Relative risk; AP: Atmospheric pressure.



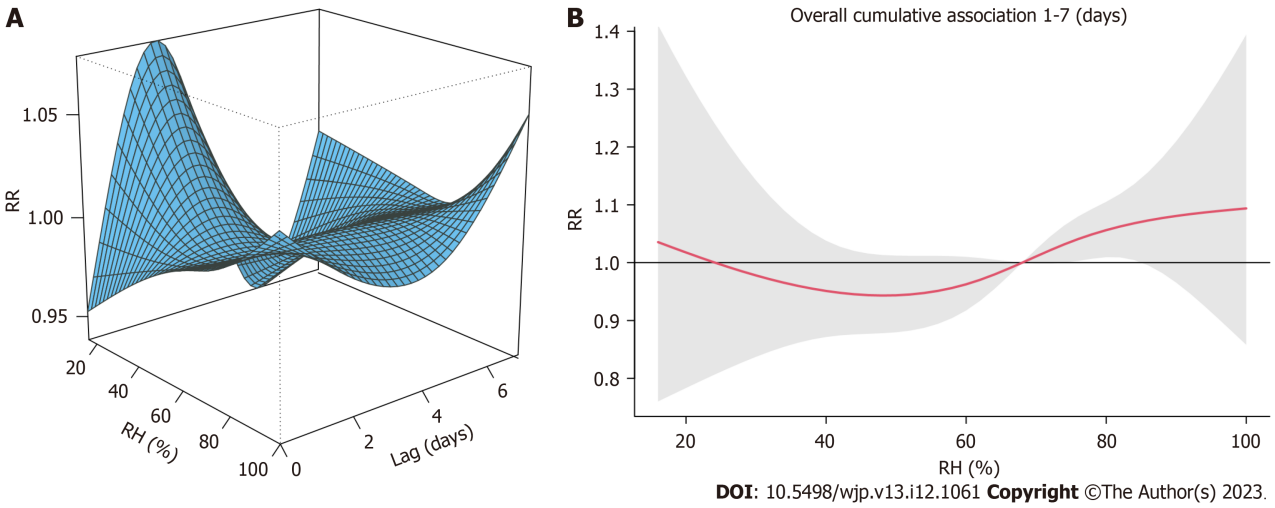
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Figure 3 Effects of wind speed on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along wind speed (WS) and lags, with reference to the median WS of 2.6 m/s; B: Overall RR of lags 1-7 by wind speed, with reference at 2.6 m/s. RR: Relative risk; WS: Wind speed.

resulted from a moderately high RH (86%) at lag 7, which increased the number of admissions by 1.09 times (95%CI: 1.01-1.17) relative to the median RH (67.9%), as shown in Figure 8.

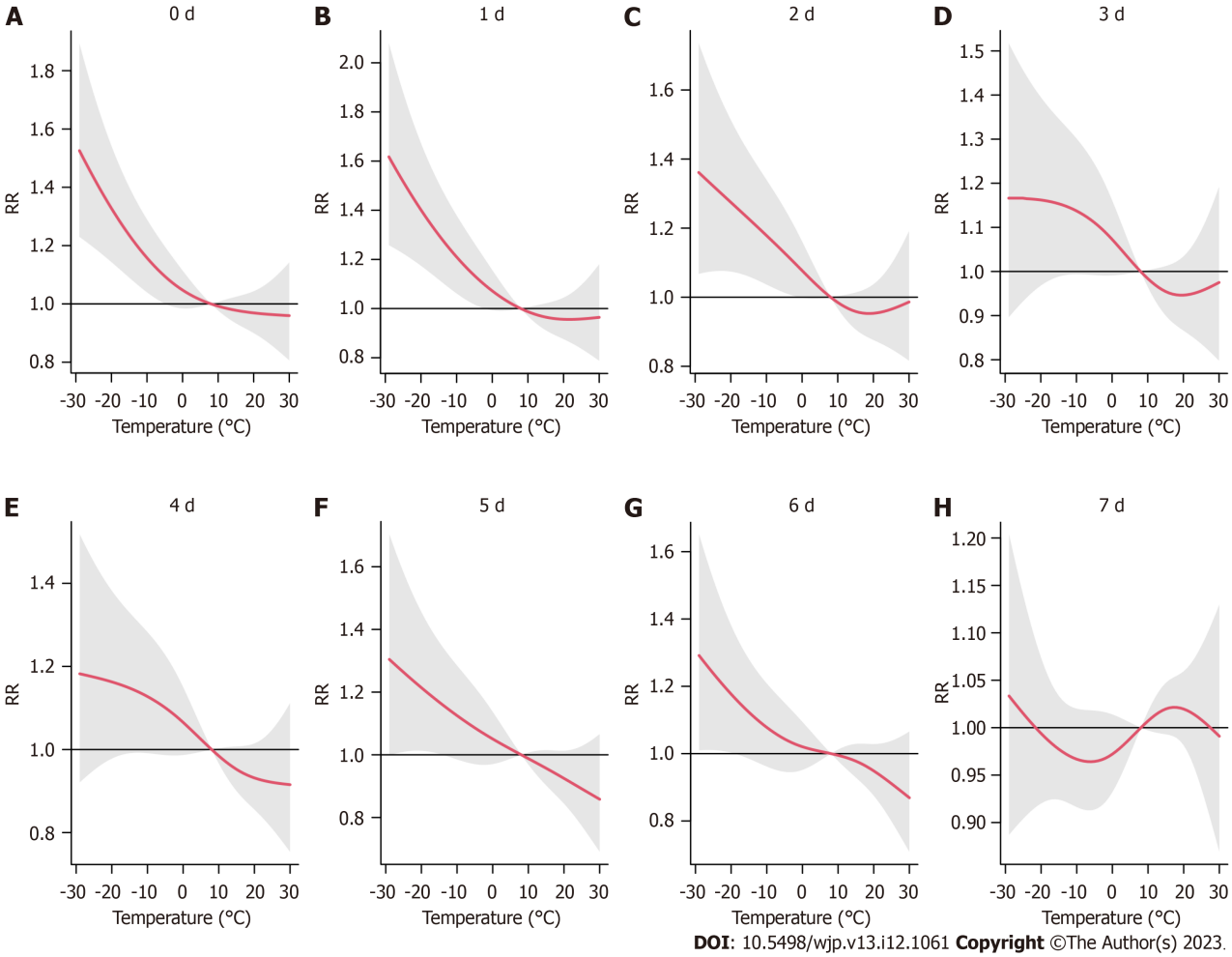
Next, the concentrations on the same day (lag 0) and 1-7 d ago (lag 1-7) of the six air pollutants were included in the time-series model. The results are shown in Figure 9. Among these air pollution variables, only NO_2 showed significant effects, and the effects of concentration increases in NO_2 at lags 0-7 were all statistically significant, despite their weakness. The cumulative exposure to air pollution was also modeled and plotted, as shown in Figure 10. Consistent with the non-cumulative results, only NO_2 exhibited a significant cumulative effect. As NO_2 accumulated, the exposure effect on daily hospital admissions for depressive disorders increased slightly and smoothly, reaching its highest value at lag 7, where RR = 1.0047 (95%CI: 1.0024-1.0071).

A bivariate response surface model was generated to analyze the interactions between environmental factors. AT significantly interacted with all pollutants included in this study, except for NO_2. As shown in Figure 11, extremely low ATs combined with high concentrations of $PM_{2.5}$ and PM_{10} increased the number of admissions for depressive disorders. Combination of low temperature, low SO_2, and of high temperature and high SO_2 affected hospital admissions. Extremely low temperatures at any CO concentration increased the admission rate. When hot, a low CO concentration had an increasing effect, whereas a high CO concentration did not. Low temperatures and high O_3 concentrations had decreasing effects. Figure 12 shows the interactions between the AP and air pollutants. The interactions between the AP and $PM_{2.5}$, CO, NO_2, and O_3_8h were statistically significant. Low APs combined with low CO, low NO_2, or high O_3 had increasing effects, whereas high APs combined with high $PM_{2.5}$, high CO, or low O_3 increased hospital admissions for depressive disorders. The interaction patterns of AP and $PM_{2.5}$/CO/NO_2 were similar; however, the pattern between AP and O_3 was the opposite. The interactions between WS and air pollutants are shown in Figure 13. SO_2 had the only significant



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Figure 4 Effects of relative humidity on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along relative humidity (RH) and lags, with reference to the median RH of 67.9%; B: Overall RR of lags 1-7 by RH, with reference at 67.9%. RR: Relative risk; RH: Relative humidity.



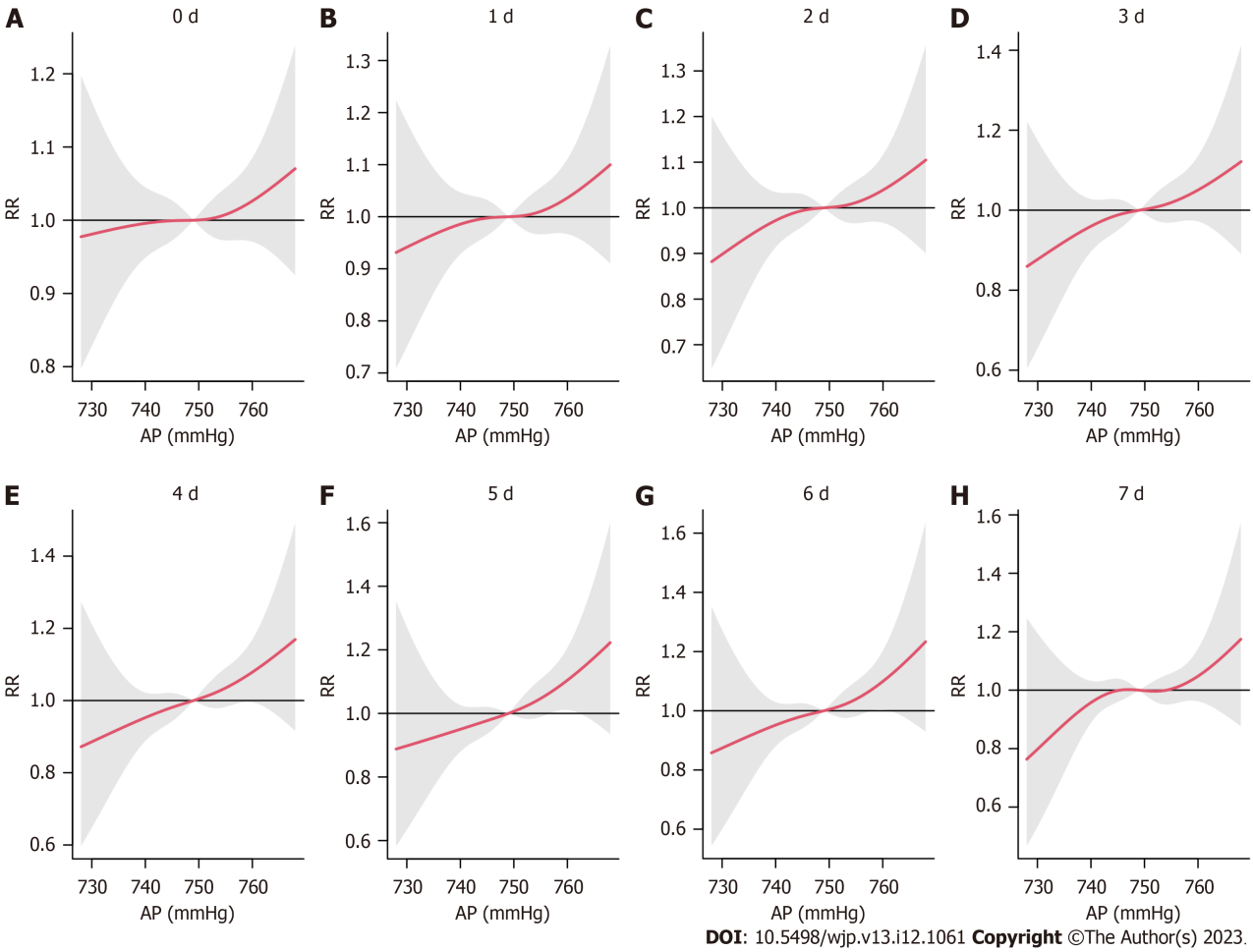
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Figure 5 Plots of relative risk by air temperature at lags 0-7. A: Relative risk (RR) by air temperature (AT) at lag 0; B: RR by AT at lag 1; C: RR by AT at lag 2; D: RR by AT at lag 3; E: RR by AT at lag 4; F: RR by AT at lag 5; G: RR by AT at lag 6; H: RR by AT at lag 7. Reference at 7.8 °C. RR: Relative risk.

Table 1 Descriptive statistics of variables (sample size = 2922 d)

Variable (unit)	mean ± SD	Percentile				
		Min	P_{25}	Median	P_{75}	Max
Admissions for depressive disorder (*n*)	28.7 ± 21.2	0	9	28	42	130
AT (℃)	5.4 ± 15.1	-29.2	-8.4	7.8	19.0	30.6
AP (mmHg)	749.3 ± 7.0	727.9	743.7	748.9	754.8	768.0
WS (m/s)	2.9 ± 1.2	0.4	2.0	2.6	3.5	9.8
RH (%)	66.2 ± 15.6	14.9	56.1	67.9	77.8	100.0
$PM_{2.5}$ (μg/m^3)	47.2 ± 54.6	0.0	16.0	29.0	58.0	906.0
PM_{10} (μg/m^3)	71.3 ± 59.3	0.0	35.0	53.0	87.0	644.0
SO_2 (μg/m^3)	22.0 ± 23.6	3.0	9.0	13.0	26.0	222.0
CO (mg/m^3)	0.9 ± 0.4	0.3	0.6	0.8	1.0	4.3
NO_2 (μg/m^3)	36.7 ± 17.8	8.0	24.0	33.0	44.0	145.0
O_3_8h (μg/m^3)	75.8 ± 34.1	0.0	50.0	71.0	96.0	253.0

AT: Air temperature; AP: Atmospheric pressure; WS: Wind speed; RH: Relative humidity; $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone.



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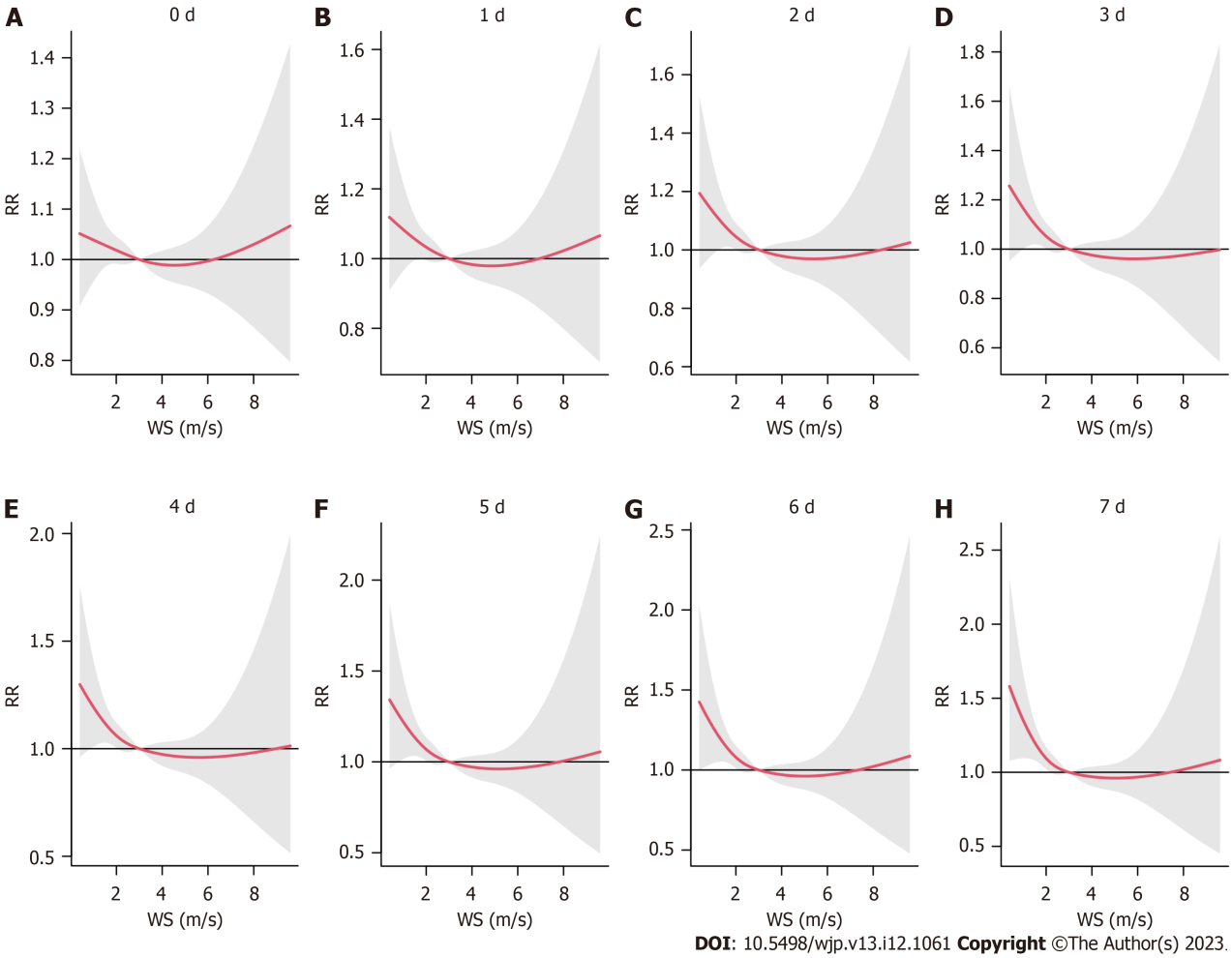
Figure 6 Plots of relative risk by atmospheric pressure at lags 0-7. A: Relative risk (RR) by atmospheric pressure (AP) at lag 0; B: RR by AP at lag 1; C: RR by AP at lag 2; D: RR by AP at lag 3; E: RR by AP at lag 4; F: RR by AP at lag 5; G: RR by AP at lag 6; H: RR by AP at lag 7. Reference at 748.9 mmHg. RR: Relative risk. AP: Atmospheric pressure.

Table 2 Spearman correlation coefficients between environmental factors

	AP	WS	RH	$PM_{2.5}$	PM_{10}	SO_2	CO	NO_2	O_3_8h
AT	-0.75[c]	0.07[c]	0.18[c]	-0.61[c]	-0.46[c]	-0.78[c]	-0.49[c]	-0.42[c]	0.60[c]
AP		-0.27[c]	-0.17[c]	0.50[c]	0.40[c]	0.62[c]	0.41[c]	0.44[c]	-0.48[c]
WS			-0.35[c]	-0.16[c]	-0.13[c]	-0.11[c]	-0.26[c]	-0.41[c]	0.17[c]
RH				-0.17[c]	-0.25[c]	-0.19[c]	-0.02	-0.06[c]	-0.21[c]
$PM_{2.5}$					0.92[c]	0.77[c]	0.78[c]	0.76[c]	-0.19[c]
PM_{10}						0.69[c]	0.71[c]	0.75[c]	-0.09[c]
SO_2							0.67[c]	0.64[c]	-0.35[c]
CO								0.76[c]	-0.21[c]
NO_2									-0.24[c]

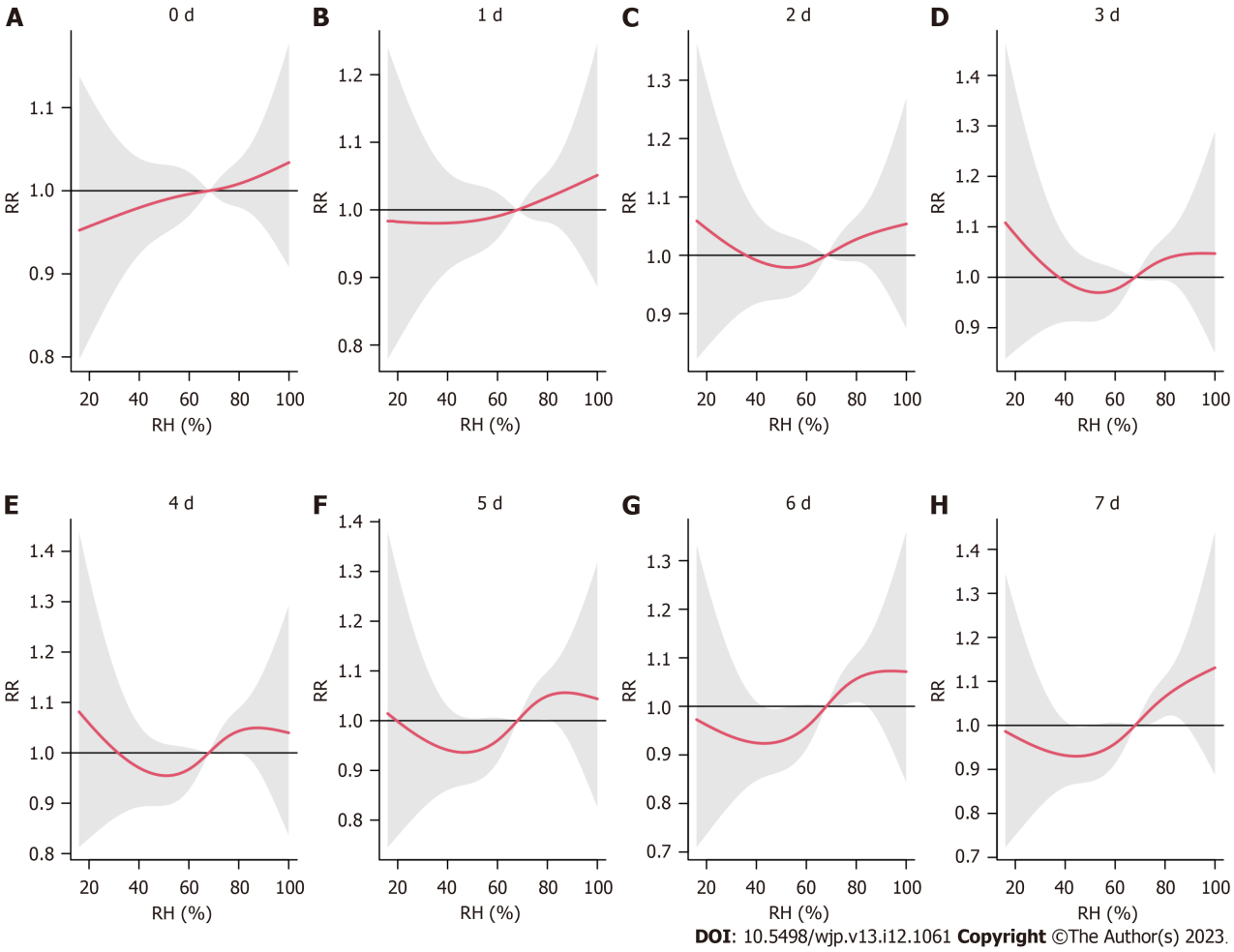
[c]$P < 0.001$.

AT: Air temperature; AP: Atmospheric pressure; WS: Wind speed; RH: Relative humidity; $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone.



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Figure 7 Plots of relative risk by wind speed at lags 0-7. A: Relative risk (RR) by wind speed (WS) at lag 0; B: RR by WS at lag 1; C: RR by WS at lag 2; D: RR by WS at lag 3; E: RR by WS at lag 4; F: RR by WS at lag 5; G: RR by WS at lag 6; H: RR by WS at lag 7. Reference at 2.6 m/s. RR: Relative risk; WS: Wind speed.



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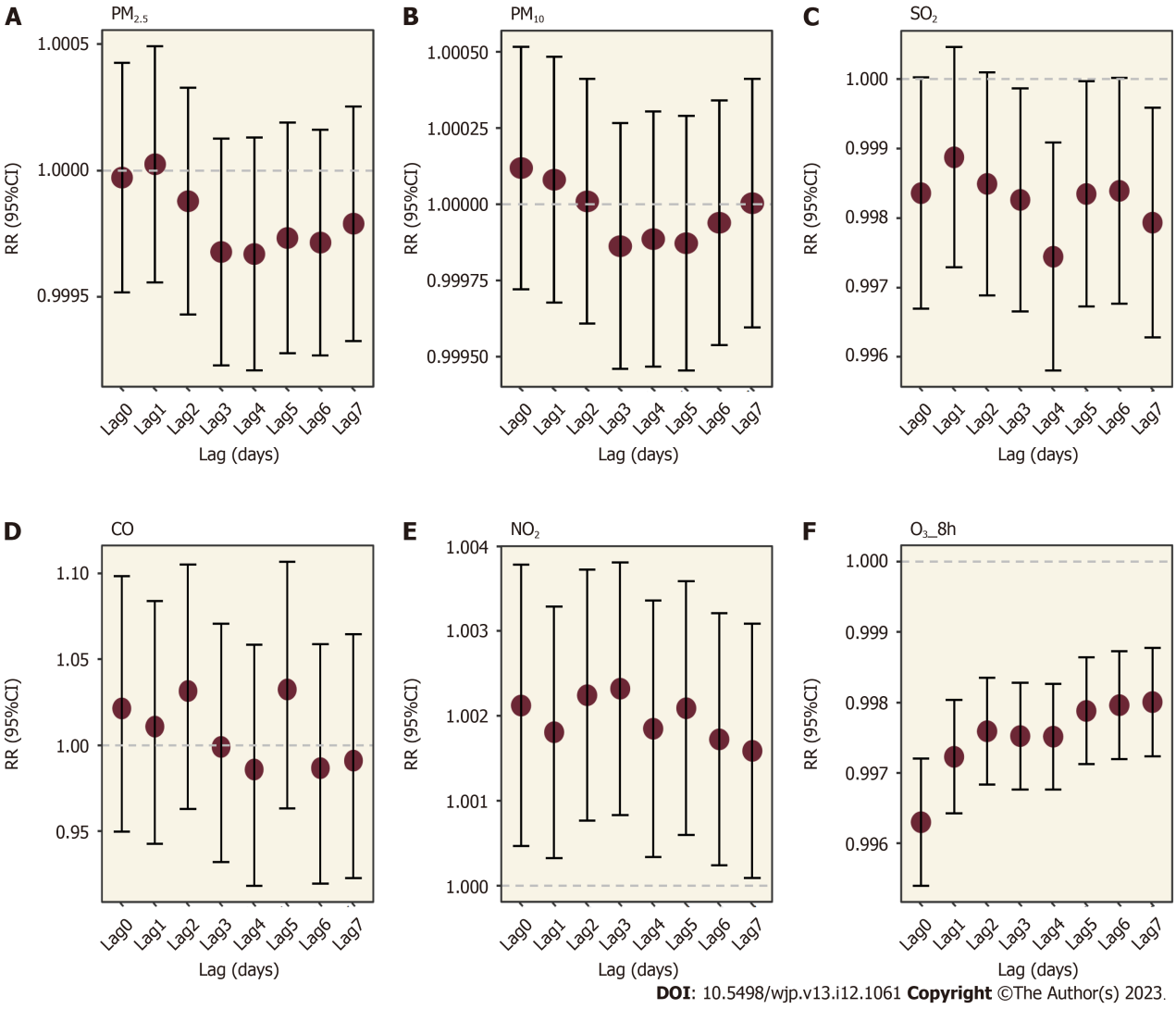
Figure 8 Plots of relative risk by relative humidity at lags 0-7. A: Relative risk (RR) by relative humidity (RH) at lag 0; B: RR by RH at lag 1; C: RR by RH at lag 2; D: RR by RH at lag 3; E: RR by RH at lag 4; F: RR by RH at lag 5; G: RR by RH at lag 6; H: RR by RH at lag 7. Reference at 67.9%. RR: Relative risk; RH: Relative humidity.

interaction effect with WS, indicating that most single effects of air pollutants were consistent at different levels of WS. Generally, when high WS and high concentrations of pollutants coexisted, hospital admissions for depressive disorders did not increase. Finally, the interactions between RH and air pollutants were analyzed, and the results are plotted in Figure 14. No significant interaction effects were found between any pair, indicating that the effects of air pollution were relatively stable across different levels of RH.

DISCUSSION

Based on daily hospital admission data for depressive disorders from 2015 to 2022 in a hospital in Harbin, China, we obtained environmental data for the same period, including meteorological and ambient air pollution data, and conducted a time-series analysis to investigate the short-term exposure effects of these environmental factors on depressive disorders. Our results showed that meteorological factors, including AT and WS, could sharply influence daily hospital admissions, while AP, RH, and air pollutant NO_2 (immediate, lagged, or cumulatively lagged) had significant but moderate or small effects. We modeled the relationship between meteorological factors and air pollution and found significant interaction effects between AT and $PM_{2.5}$/PM_{10}/SO_2/CO/O_3_8 h, AP and $PM_{2.5}$/CO/NO_2/O_3_8 h, and WS and SO_2.

Specifically, we found that the risk of depressive disorder admission increases by 53% when an extremely low temperature (-29 ℃, for Harbin) occurs. This finding was consistent with the results of a previous study conducted in Europe[8], but contrary to most similar studies[5,14,33-35], where increased or high AT was associated with increased depressive symptoms or higher hospital admissions. This inconsistency may have resulted from regional differences in the areas of interest selected by each study. Harbin City (45°25′-45°30′N, 126°20–126°25′E) is located in Northeast China and has a typical continental monsoon climate. The highest temperature in the study period was 30.6 ℃, indicating that it is never excessively hot in Harbin, unlike in Hong Kong[5] or Shanghai[33]. From reference[6], we know that both low and high temperatures might be important drivers of morbidity in mental disorders and that lower temperatures may have a more general and widespread effect on cause-specific morbidity. The result in Europe[8] even showed a protective



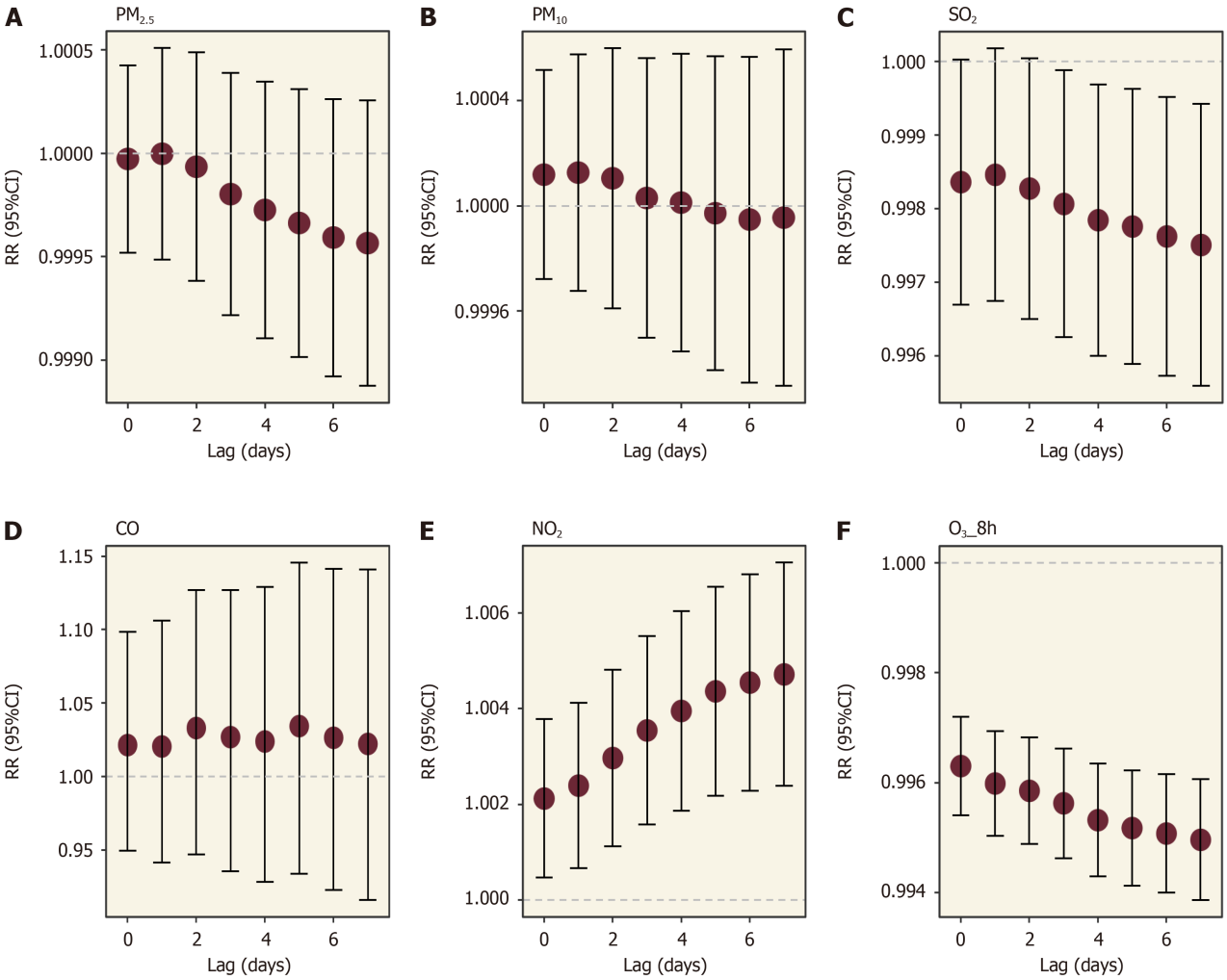
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Figure 9 Plots of relative risk by air pollutant concentrations at lags 0-7. A: Relative risk (RR) by fine particles concentrations at lags 0-7; B: RR by inhalable particles concentrations at lags 0-7; C: RR by sulfur dioxide$_2$ concentrations at lags 0-7; D: RR by carbon monoxide concentrations at lags 0-7; E: RR by nitrogen dioxide concentrations at lags 0-7; F: RR by maximum 8-h average concentration of ozone concentrations at lags 0-7. $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone; RR: Relative risk.

impact of a higher AT (> 14.2 ℃), which may serve as a reference for explaining the zero effects of a higher temperature in Harbin. A famous nickname for Harbin City is "Ice City," indicating its freezing coldness in winter. Studies have shown that exercise interventions[15] and frequent visits to outdoor green spaces[17] effectively improve depression symptoms. Therefore, extremely low temperatures can negatively affect depressive symptoms by limiting outdoor exercises and visits to green spaces. Furthermore, low temperatures usually co-exist with insufficient sunlight in winter, and reduced sunlight exposure, both in intensity and duration, is related to an increased risk of depression, according to previous studies[22,36]. Despite this inconsistency with most similar studies, this study confirmed the importance of AT in depressive admissions.

In addition, we found a 58% increase in depressive disorder admissions when the WS approached zero. We propose two possible mechanisms underlying the effect of low WS. First, as coal-fired heating in the cold period always causes severe air pollution in Harbin[37,38], low WS would worsen the air pollution. Air pollution-induced inflammation of the respiratory airways is associated with depression in vulnerable individuals[39]. Severe air pollution may also decrease outdoor activities and sunlight exposure, thereby increasing the risk of depressive disorder[40]. Hence, low WS during cold winters may be associated with depressive symptoms caused by severe air pollution. Second, a previous study showed that during warmer periods, warm and dry winds have an increasing effect on the concentration of positive ions in the atmosphere, which increases blood and brain serotonin levels[8]. Low WS may not provide this improving effect on depressive symptoms.

We also found relatively small effects of AP, RH, and the air pollutant NO_2. These results are consistent with previous studies, where high RH levels seem to be pertinent to suicide risk[41] and nitrogen oxides increase the risk of mental health problems, probably *via* mechanisms of inflammation and neuronal injury[35].



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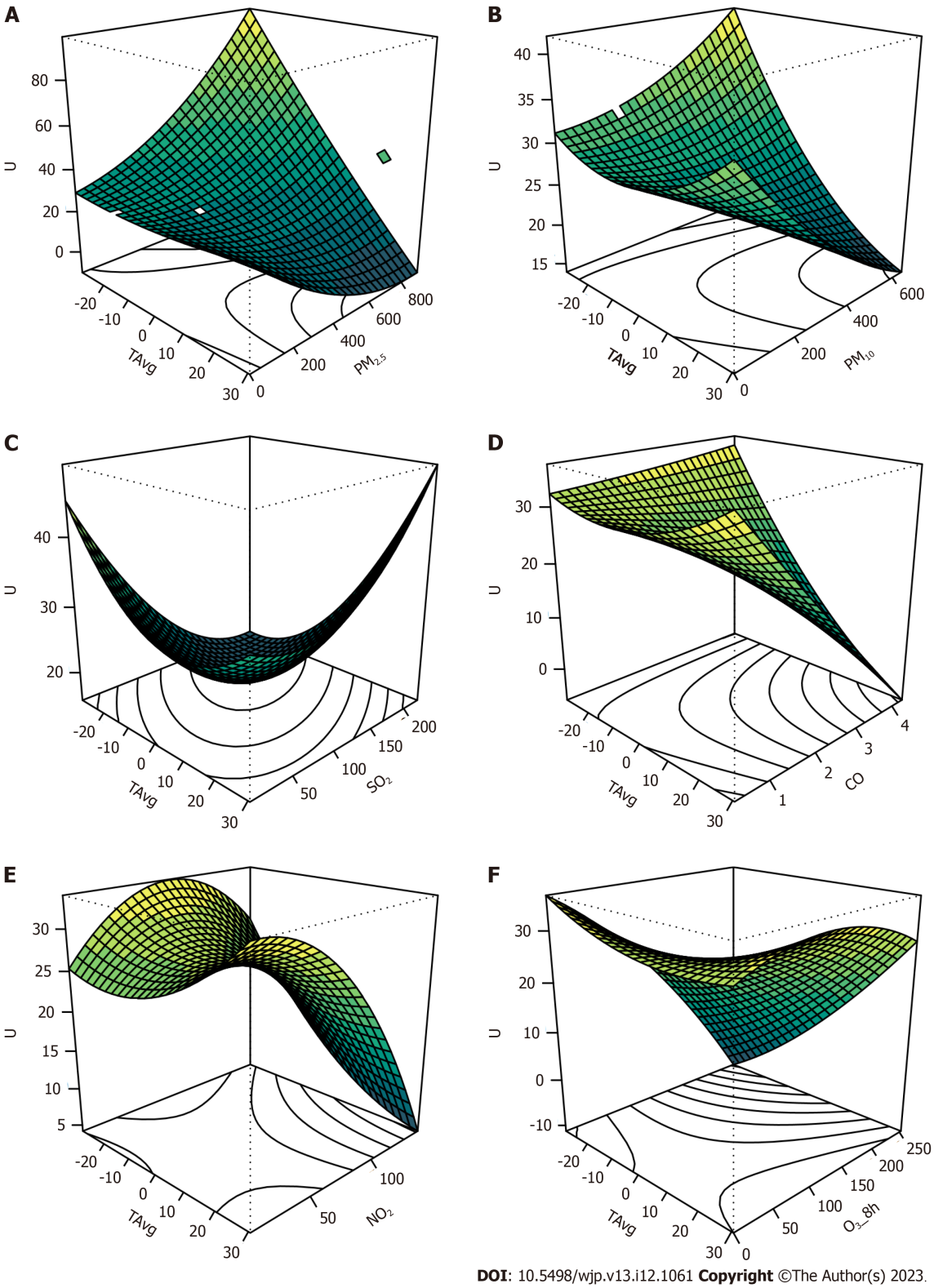
Figure 10 Plots of relative risk by cumulative air pollutant concentrations for lags 0-7. A: Relative risk (RR) by cumulative fine particles concentrations at lags 0-7; B: RR by cumulative inhalable particles concentrations at lags 0-7; C: RR by cumulative sulfur dioxide concentrations at lags 0-7; D: RR by cumulative carbon monoxide concentrations at lags 0-7; E: RR by cumulative nitrogen dioxide concentrations at lags 0-7; F: RR by cumulative maximum 8-h average concentration of ozone concentrations at lags 0-7. $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone; RR: Relative risk.

The distinctive results of this study were the interactions between AT and $PM_{2.5}$/PM_{10}/SO_2/CO/O_3_8 h, AP and $PM_{2.5}$/CO/NO_2/O_3_8 h, and WS and SO_2. After carefully inspecting the patterns of these interactions, we assumed that most interactions corresponded to the relationship between the increased risk of depressive disorder and severe air pollution caused by coal-fired heating. In most significant interactions, typical meteorological factor levels in winter (including low AT and high AP) combined with high levels of air pollutants were associated with depressive symptoms. The interaction between WS and SO_2 was the same, as both high WS plus low SO_2 and low WS plus high SO_2 seemed unfavorable for outdoor activities and sunlight exposure. The increasing effect of low WS plus low SO_2 may appear during warmer periods, as low WS does not improve serotonin levels. The cases of O_3 were different from those of the others. We assumed that the reason for this inconsistency between O_3 and other air pollutants was seasonal differences. The O_3 concentration is typically high in the summer, whereas the concentrations of other pollutants are high in the winter.

The strength of our study lies in the precise effects we modeled and measured, especially the interaction between meteorological factors and ambient air pollution. Although our results indicate the effects of environmental factors on hospital admissions for depressive disorders, they are inconsistent with most similar studies and need to be replicated in other methodologically superior studies. The results cannot be generalized to the entire population of China because the sample came from only one northeastern city and urban population. Patient information was insufficient, which limited further analyses.

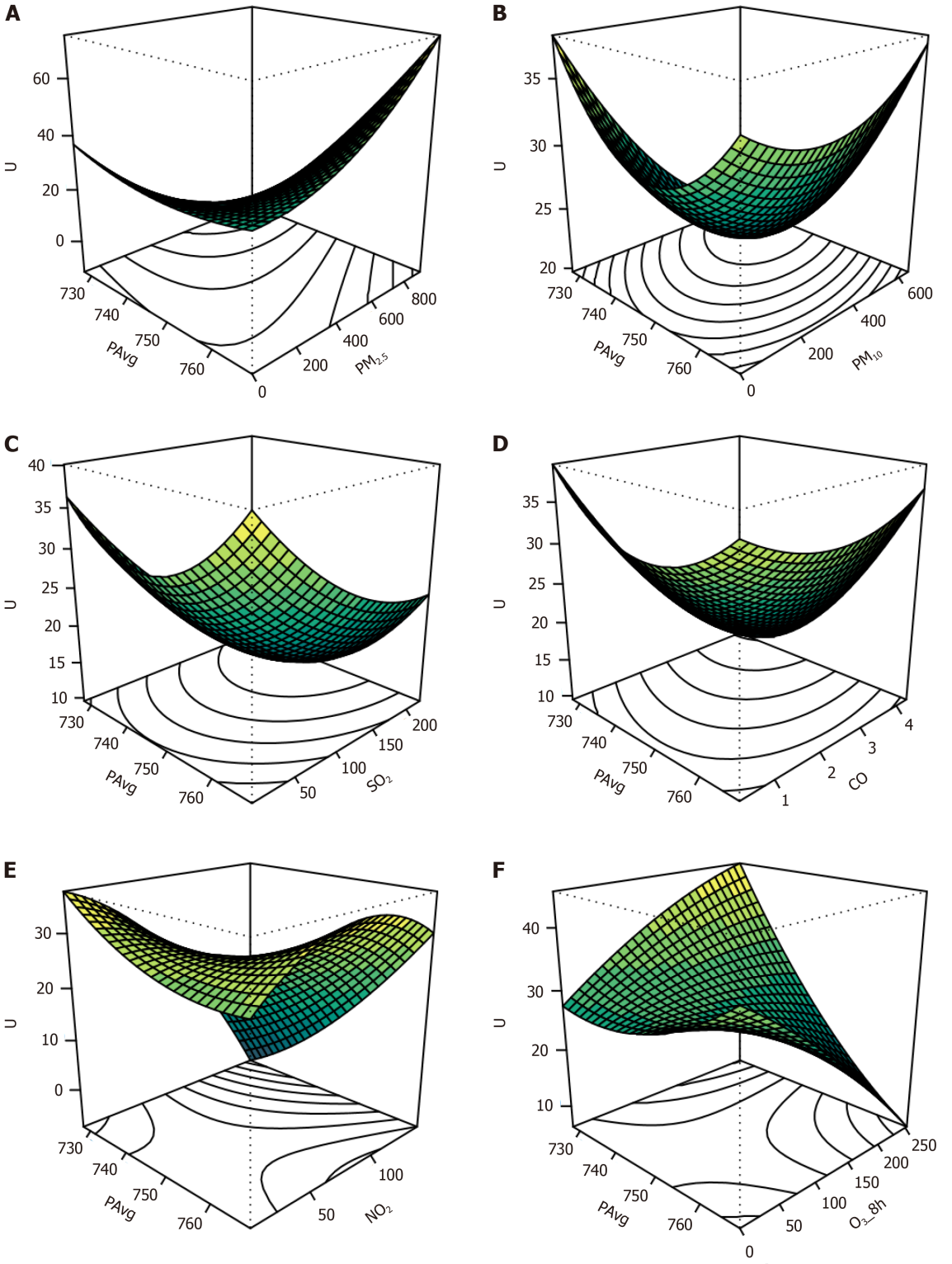
CONCLUSION

Our study suggests that meteorological factors and the air pollutant NO_2 affect daily hospital admissions for depressive disorders and that interaction effects exist between meteorological factors and ambient air pollution. Clinicians and



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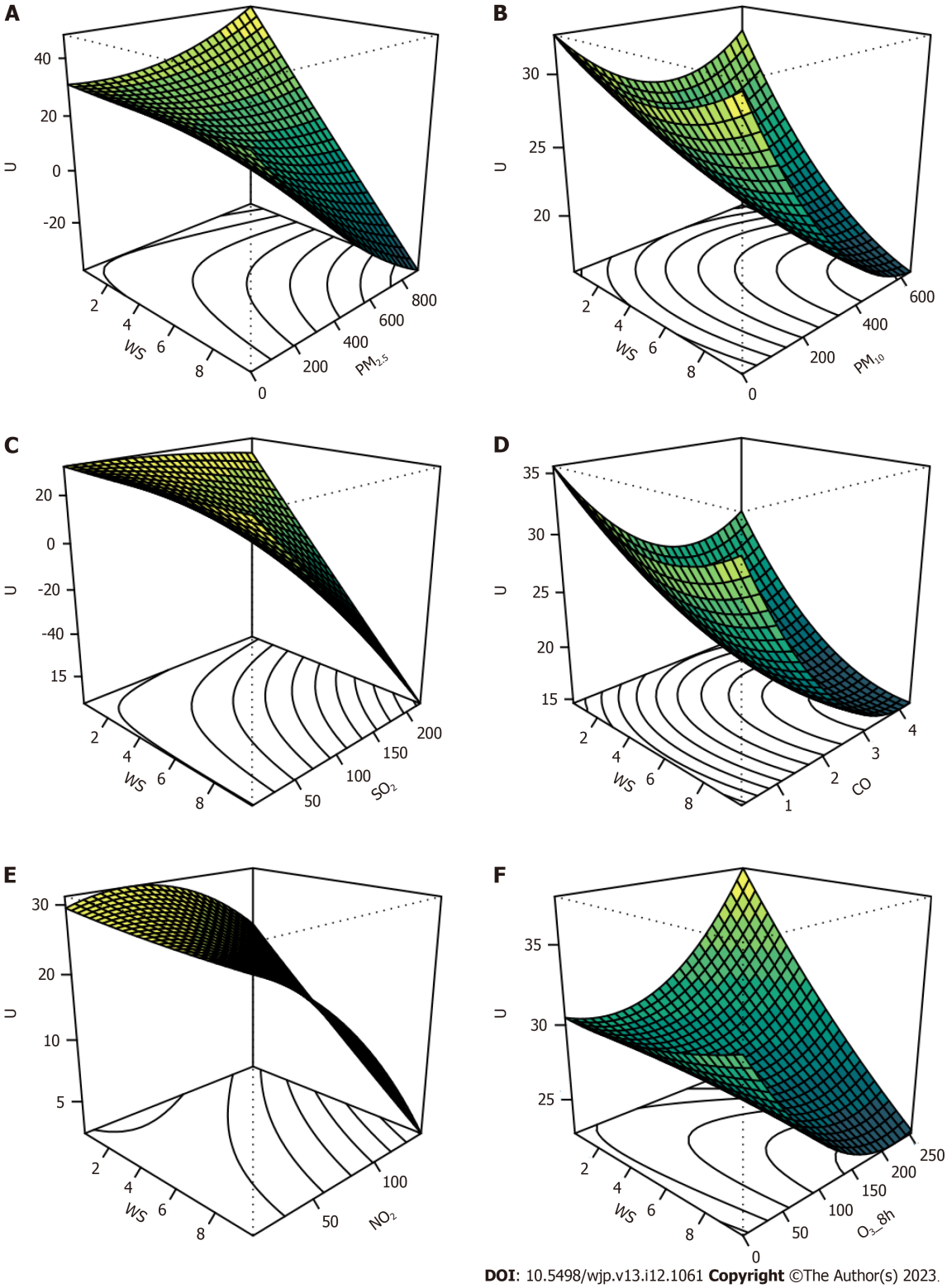
Figure 11 3D perspective plots of the interaction effects between air temperature and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between air temperature (AT) and fine particles; B: Interaction between AT and inhalable particles; C: Interaction between AT and sulfur dioxide; D: Interaction between AT and carbon monoxide; E: Interaction between AT and nitrogen dioxide; F: Interaction between AT and maximum 8-h average concentration of ozone. AT: Air temperature; $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone.



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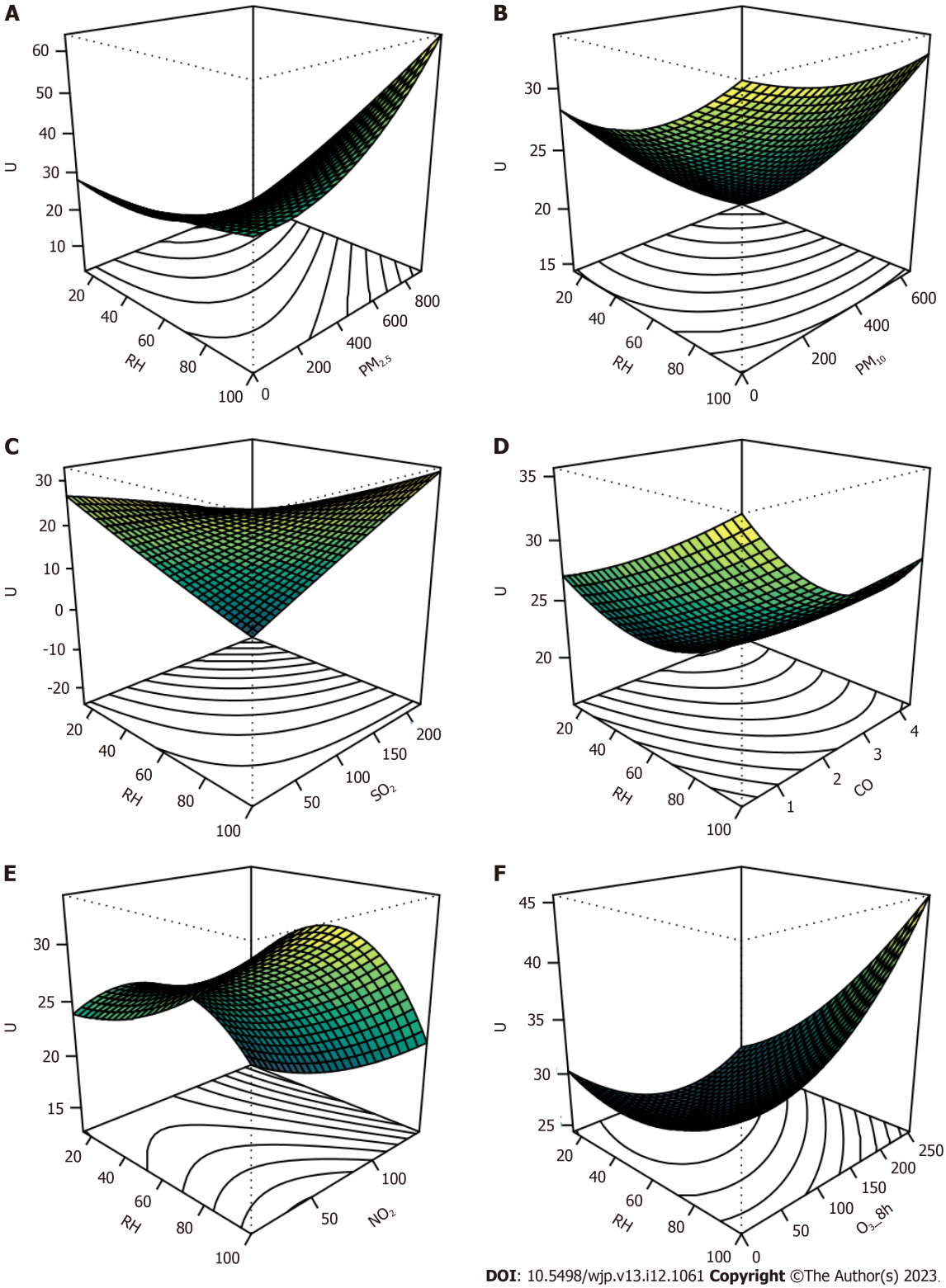
Figure 12 3D perspective plots of the interaction effects between atmospheric pressure and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between atmospheric pressure (AP) and fine particles; B: Interaction between AP and inhalable particles; C: Interaction between AP and sulfur dioxide; D: Interaction between AP and carbon monoxide; E: Interaction between AP and nitrogen dioxide; F: Interaction between AP and maximum 8-h average concentration of ozone. AP: Atmospheric pressure; $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone.

patients are encouraged to pay more attention to the environmental effects on depressive symptoms. More stringent air quality control measures may be helpful to protect public mental health. Further studies involving more cities in China and a larger sample should be conducted to enable generalization. Thorough studies into the underlying mechanisms for environment impacting mental health are also warranted.



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Figure 13 3D perspective plots of the interaction effects between wind speed and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between wind speed (WS) and fine particles; B: Interaction between WS and inhalable particles; C: Interaction between WS and sulfur dioxide; D: Interaction between WS and carbon monoxide; E: Interaction between WS and nitrogen dioxide; F: Interaction between WS and maximum 8-h average concentration of ozone. WS: Wind speed; $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone.



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Figure 14 3D perspective plots of the interaction effects between relative humidity and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between relative humidity (RH) and fine particles; B: Interaction between RH and inhalable particles; C: Interaction between RH and sulfur dioxide; D: Interaction between RH and carbon monoxide; E: Interaction between RH and nitrogen dioxide; F: Interaction between RH and maximum 8-h average concentration of ozone. RH: Relative humidity; $PM_{2.5}$: Fine particles; PM_{10}: Inhalable particles; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3_8h: Maximum 8-h average concentration of ozone.

ARTICLE HIGHLIGHTS

Research background

Environmental factors have been shown to affect individual mental health; however, the relationships and effects of different environmental factors in relatively cold areas have not yet been clarified.

Research motivation

We studied the effects of environmental factors, including their interaction effects, on daily hospital admissions for depressive disorders, aiming to discover the patterns of interaction between various environmental factors and provide regional references for this research field.

Research objectives

To investigate the single and interaction effects of environmental factors, we modeled, measured, and plotted these potential effects and added evidence to explore the complex relationship between environmental factors and human mental health.

Research methods

We performed a retrospective study using data from Harbin, China between 2015 and 2022, including daily hospital admissions for depressive disorders, meteorological data, and air pollution data. A time-series analysis was conducted using generalized additive models with quasi-Poisson regression to measure the effect of each single factor on depression. A bivariate response surface model was used to model the interaction effects of different factors. Our data came from a higher-latitude area, offering an opportunity to investigate regional differences in relationship patterns and the effects of environmental factors.

Research results

Our results showed that air temperature and wind speed influenced daily hospital admissions. Extremely low temperatures and wind speeds could increase daily hospital admissions for depressive disorders by approximately 50%. atmospheric pressure, relative humidity, and the air pollutant nitrogen dioxide had significant but moderate effects. Interaction effects between three meteorological factors and six air pollutants were discovered.

Research conclusions

Meteorological factors and air pollutants have single and interaction effects on daily hospital admissions for depressive disorders, and the effect pattern may be related to coal-fired heating in winter.

Research perspectives

Specific mechanisms behind the complex relationships of environmental factors are to be studied.

FOOTNOTES

Author contributions: Hu T designed and performed the research and wrote the paper; Guo BB designed the research and supervised the report; and Xu ZY, Wang J, and Su Y provided clinical advice.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of The First Psychiatric Hospital of Harbin.

Informed consent statement: This paper is a retrospective study that collects information on cases that have already occurred in the past, is analysed anonymously, does not expose patients' private information, does not cause harm to patients, and successful application for waiver of informed consent has therefore been made.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Analysis of influencing factors and the construction of predictive models for postpartum depression in older pregnant women

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Abstract

BACKGROUND

Changes in China's fertility policy have led to a significant increase in older pregnant women. At present, there is a lack of analysis of influencing factors and research on predictive models for postpartum depression (PPD) in older pregnant women.

AIM

To analysis the influencing factors and the construction of predictive models for PPD in older pregnant women.

METHODS

By adopting a cross-sectional survey research design, 239 older pregnant women (≥ 35 years old) who underwent obstetric examinations and gave birth at Suzhou Ninth People's Hospital from February 2022 to July 2023 were selected as the research subjects. When postpartum women of advanced maternal age came to the hospital for follow-up 42 d after birth, the Edinburgh PPD Scale (EPDS) was used to assess the presence of PPD symptoms. The women were divided into a PPD group and a no-PPD group. Two sets of data were collected for analysis, and a prediction model was constructed. The performance of the predictive model was evaluated using receiver operating characteristic (ROC) analysis and the Hosmer-Lemeshow goodness-of-fit test.

RESULTS

On the 42nd day after delivery, 51 of 239 older pregnant women were evaluated with the EPDS scale and found to have depressive symptoms. The incidence rate was 21.34% (51/239). There were statistically significant differences between the PPD group and the no-PPD group in terms of education level (P = 0.004), family relationships (P = 0.001), pregnancy complications (P = 0.019), and mother–infant separation after birth (P = 0.002). Multivariate logistic regression analysis showed that a high school education and below, poor family relationships, pregnancy

complications, and the separation of the mother and baby after birth were influencing factors for PPD in older pregnant women ($P < 0.05$). Based on the influencing factors, the following model equation was developed: Logit (P) = 0.729 × education level + 0.942 × family relationship + 1.137 × pregnancy complications + 1.285 × separation of the mother and infant after birth -6.671. The area under the ROC curve of this prediction model was 0.873 (95%CI: 0.821-0.924), the sensitivity was 0.871, and the specificity was 0.815. The deviation between the value predicted by the model and the actual value through the Hosmer-Lemeshow goodness-of-fit test was not statistically significant ($\chi^2 = 2.749$, $P = 0.638$), indicating that the model did not show an overfitting phenomenon.

CONCLUSION

The risk of PPD among older pregnant women is influenced by educational level, family relationships, pregnancy complications, and the separation of the mother and baby after birth. A prediction model based on these factors can effectively predict the risk of PPD in older pregnant women.

Key Words: Older pregnant women; Postpartum depression; Influencing factors; Prediction model

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Core Tip: Older pregnant women are more likely to develop postpartum depression (PPD) than younger pregnant women. PPD can harm the physical and mental health of pregnant women, offspring development, and family and social harmony. Here, we investigated the PPD status of 239 older pregnant women. Based on whether the older pregnant women experienced depression 42 d postpartum, we divided them into a PPD group and a no-PPD group. By conducting statistical analysis on two sets of data and constructing a prediction model, we examined the issue of how medical personnel can effectively assess the PPD risk of older pregnant women.

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INTRODUCTION

Postpartum depression (PPD) is a postpartum mental condition characterized by anxiety, irritability, and extreme depression. In severe cases, hallucinations or suicidal tendencies may occur[1]. PPD not only harms the physical and mental health of pregnant women but also has adverse effects on offspring development, families, and society[2]. Related research reports show that the incidence of PPD among younger pregnant women in China is 14.7%. The incidence of PPD in older pregnant women (≥ 35 years old) is as high as 36.9%[3]. There are some recent studies on PPD in pregnant women, but they are all based on analyses of mental illness history, family relationships, and other aspects[4,5]. There is a lack of exploration on pregnancy complications and the separation of mothers and babies after birth. This results in inadequate clinical measures to prevent PPD, and there is a lack of reporting on predictive models. This study combined the overall situation before, during, and after childbirth to understand the influencing factors of PPD in older pregnant women and construct a risk prediction model to provide guidance for obstetricians in predicting the risk of PPD in older pregnant women and developing treatment measures.

MATERIALS AND METHODS

Patient characteristics

Adopting a cross-sectional survey research design, 239 older pregnant women (≥ 35 years old) who underwent obstetric examinations and gave birth in our hospital from February 2022 to July 2023 were selected as the research subjects. According to the Edinburgh PPD Scale (EPDS), the presence or absence of PPD symptoms was measured at 42 d postpartum, and the older pregnant women were divided into a PPD group and a no-PPD group. This study was approved by the Medical Ethics Committee of Suzhou Ninth People's Hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Women with a gestational age ≥ 37 wk at delivery, a single birth, and natural conception; (2) women with normal consciousness and intelligence; (3) women without adverse pregnancy outcomes (stillbirth, abortion, deformity); (4) women who were informed of this study and signed an informed consent form; and (5) women who were evaluated with the EPDS at 42 d postpartum. The exclusion criteria were as follows: (1) Women with comorbid malignant tumors; (2) women with trauma or infection before delivery; (3) women diagnosed with

depression during any depression screening during pregnancy (early, middle, late) or the prenatal period (prior to delivery)[6]; and (4) women with past mental illness.

Survey methods

General information: By creating a general data collection form, age, education level, birth history, pregnancy complications (pregnancy-induced hypertension, pregnancy-induced diabetes, *etc.*), delivery mode, separation of the mother and infant after birth (referring to the newborn needing to be admitted to the neonatal department for treatment after birth), neonatal feeding mode and other information of the older pregnant women were collected.

Family relationships: The Chinese version of the Family Adaptability Cohesion Environment Scale II-CV[7] was used to evaluate the family relationships of the older pregnant women. This scale mainly evaluates intimacy and adaptability. Intimacy refers to the emotional connection between a mother and her family members. Adaptability refers to the ability of a mother to adapt to the different developmental stages of her family and family situation. This scale consists of 30 items. The total score ranges from 30 to 150 points, and items are scored using a 5-point likert-type (1-5 points) scoring method. The higher the score is, the better the family relationship. In this study, a score of ≤ 70 indicates a lack of harmonious family relationships; a score of > 70 indicates a harmonious family relationship.

PPD diagnosis: At each pregnant woman's follow-up visit at our obstetric clinic on the 42nd day postpartum, we evaluated whether she had PPD symptoms using the EPDS. The scale consists of 10 items, and the total score is 30 points. When the EPDS score of an older mother is ≥ 9 points, it indicates the presence of PPD symptoms[8].

Statistical procedure

Using SPSS 25.0 software for data analysis, the counting data are expressed in terms of the rate and composition ratio [*n* (%)]. The two groups were compared and subjected to the χ^2 test. The influencing factors of PPD in older pregnant women were analyzed through multiple logistic regression analysis, and predictive model equations were built based on the influencing factors.

The area under the receiver operating characteristic (ROC) area under curve (AUC) was used to evaluate the predictive efficiency of the model, and the Hosmer-Lemeshow goodness-of-fit test was used to evaluate whether the prediction model showed an overfitting phenomenon. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

The incidence and univariate analysis of PPD in older pregnant women

On the 42nd d after delivery, 239 older pregnant women who attended their outpatient follow-up were included, and 51 were found to have depressive symptoms (PPD group) after evaluation with the EPDS. The incidence rate was 21.34% (51/239); 188 women (no-PPD group) had no depressive symptoms. The comparison between the PPD group and the no-PPD group showed statistically significant differences in terms of education level ($\chi^2 = 8.290$, $P = 0.004$), family relationships ($\chi^2 = 10.672$, $P = 0.001$), pregnancy complications ($\chi^2 = 5.520$, $P = 0.019$), and mother–infant separation after birth ($\chi^2 = 9.681$, $P = 0.002$) (Table 1).

Multivariate logistic regression analysis of PPD in older pregnant women

The dependent variable was whether the older pregnant women had symptoms of PPD at 42 d postpartum (0 = no; 1 = yes). Features with statistical significance in univariate analysis (education level, family relationships, pregnancy complications, and the separation of the mother and infant after birth) were included as independent variables, and the assigned values are shown in Table 2. After multiple factor logistic regression analysis, it was found that a high school education and below, poor family relationships, pregnancy complications, and the separation of the mother and baby after birth were the influencing factors for PPD in older pregnant women ($P < 0.05$) (Table 3).

Construction of a risk prediction model for PPD in older pregnant women

The prediction model was constructed based on the regression coefficients and constant terms shown in Table 2 to obtain the following equation: Logit (P) = 0.729 × education level (0 = college or higher; 1 = high school and below) + 0.942 × family relationships (0 = harmony; 1 = disharmony) + 1.137 × pregnancy complications (0 = no; 1 = yes) + 1.285 × separation of the mother and infant after birth (0 = no; 1 = yes) -6.671. Using the predicted probability value of the model as the test variable, the state variable was the presence or absence of PPD in the older mothers. ROC curves were drawn to analyze and predict the performance of the model. The AUC area under the ROC curve of the prediction model was 0.873 (95%CI: 0.821-0.924), the sensitivity was 0.871, and the specificity was 0.815, which indicates that the model has good differentiation ability (Figure 1). The deviation between the predicted value of the model and the actual value through the Hosmer-Lemeshow goodness-of-fit test was not statistically significant ($\chi^2 = 2.749$, $P = 0.638$), indicating that the model showed no overfitting phenomenon.

Table 1 Single factor analysis of postpartum depression in older pregnant women (*n* = 239)

Characteristics	PPD group (*n* = 51)		No-PPD group (*n* = 188)		χ^2	*P* value
	n	Percent	*n*	Percent		
Age (yr)					2.145	0.143
35-40	40	78.4	163	86.7		
> 40	11	21.6	25	13.3		
Education level					8.290	0.004
High school and below	33	64.7	79	42.0		
College or higher	18	35.3	109	58.0		
Family relationships					10.672	0.001
Harmony	19	37.3	118	62.8		
Disharmony	32	62.7	70	37.2		
Reproductive history					0.920	0.337
Primipara	14	27.5	65	34.6		
Multipara	37	72.5	123	65.4		
Pregnancy complications					5.520	0.019
Yes	20	39.2	43	22.9		
No	31	60.8	145	77.1		
Delivery method					0.045	0.832
Spontaneous labor	22	43.1	78	41.5		
Cesarean section	29	56.9	110	58.5		
Separation of the mother and infant after birth					9.681	0.002
Yes	12	23.5	15	8.0		
No	39	76.5	173	92.0		
Feeding methods of newborns					4.838	0.089
Artificial feeding	11	21.6	19	10.1		
Mixed feeding	18	35.3	79	42.0		
Exclusive breastfeeding	22	43.1	90	47.9		

PPD: Postpartum depression.

Table 2 Variable assignment description

Variable	Description of valuation
Education level	0 = college or higher; 1 = high school and below
Family relationships	0 = harmonious; 1 = disharmony
Pregnancy complications	0= no; 1= yes
Separation of the mother and infant after birth	0= no; 1= yes

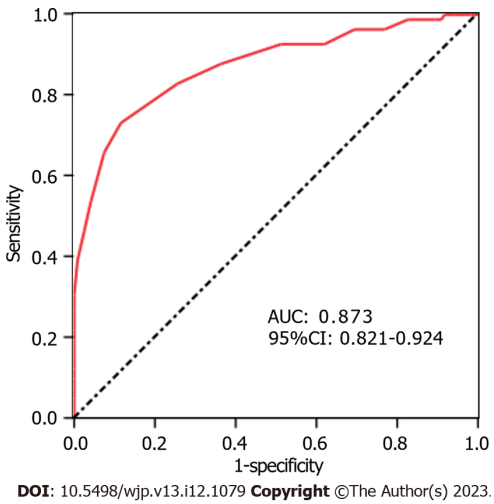
DISCUSSION

China's fertility policy is open, which has resulted in a significant increase in the number of older pregnant women[9]. The incidence of PPD among older pregnant women is relatively high. Some influencing factors for the occurrence of PPD in older pregnant women were identified, and a model was constructed to predict the PPD risk of older pregnant women early, help to take early preventive measures, and reduce the incidence of PPD in older pregnant women.

Table 3 Multivariate logistic regression analysis results of postpartum depression in older pregnant women

Variable	β	SE	Wald χ^2	*P* value	OR (95%CI)
High school and below	0.729	0.279	6.827	0.009	2.073 (1.199-3.582)
Incompatible family relationships	0.942	0.349	7.285	0.007	2.565 (1.294-5.083)
Pregnancy complications	1.137	0.414	7.543	0.006	3.117 (1.385-7.015)
Separation of the mother and infant after birth	1.285	0.416	9.541	0.002	3.615 (1.599-8.166)
Constant	-6.671	1.884	12.538	< 0.001	

SE: Standard error; OR: Odds ratio.



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Figure 1 Receiver operating characteristic curve evaluation of the postpartum depression risk prediction model for older pregnant women. AUC: Area under curve.

An analysis of the Chinese PPD population showed that the incidence of PPD was highest within 6 wk after delivery (the postpartum period)[10]. This study found that the incidence of PPD in older pregnant women at 42 d postpartum was 21.34%, which is within the scope of literature reports[11,12]. PPD symptoms in older pregnant women may be caused by various factors. This study further found that a high school education and below, poor family relationships, pregnancy complications, and the separation of the mother and baby after birth were all factors affecting PPD in older pregnant women. Some possible reasons are as follows: (1) Studies have shown that pregnant women with low education levels are prone to fear of childbirth[13]. When a mother has the psychological characteristics of fea, poor cognitive integration, a lack of proactive ways to seek help, and is extremely prone to negative emotions, if she cannot find a positive way to alleviate her fear, she may have a low self-evaluation of postpartum care for her newborn, have an increased psychological burden, and develop PPD. Additionally, a low education level and a poor living environment and family economic situation may also affect PPD risk to some extent[14]. The pressure of raising young children is high [15], quality of life is affected[16], and it is easy to generate negative emotions, which triggers PPD symptoms; (2) family relationships play an important role in the family[17]. A woman usually needs care and attention from her mother-in-law after childbirth[18]; differences in cognition between the two generations may result in differences of opinion regarding the care of the newborn and even conflicts. This invisibly causes psychological pressure and burdens for the new mother [19]. As a result, the family environment is not harmonious, which often increases the mental burden on mothers[20]. Severe cases may result in the mother not receiving sufficient family support, thus increasing her risk of PPD occurrence; (3) older pregnant women tend to have diabetes and hypertension during pregnancy[21]. Research shows that, women diagnosed with pregnancy induced hypertension were more likely to have depressive symptoms than their normotensive counterparts[22]. These pregnancy complications not only increase the risk of PPD[23] but also increase the risk of complications such as postpartum infections and bleeding[24]. Studies have shown that puerperal infection events are significantly correlated with PPD[25]. Which increases the risk of PPD and affects the physical recovery of the mother. Therefore, pregnancy complications are an important factor in increasing PPD; and (4) the health status of newborns is a key concern for mothers and their families. Previous studies have shown that infant health is a contributing factor to PPD in postpartum women[26]. This may be due to the combination of other diseases at birth and the need for a newborn to be transferred to a neonatal department for relevant monitoring and treatment[27], increase maternal concerns about the health status of their children, causing psychological storage of certain negative information, aggravate psychological stress, making it easy for mothers to be emotionally affected by these negative information, increase the risk of

postpartum PPD. At the same time, when the newborn is complicated with diseases, the family has to bear a large amount of medical expenses and increase the family burden[28], which significantly increases the probability of PPD in the maternal.

The development of a good prediction model lies in screening effective indicators. This study analyzed the influencing factors of PPD in older pregnant women through multiple logistic regression analysis and built a prediction model based on influencing factors. After analysis, it was found that the area under the ROC curve of the prediction model was 0.873, which indicated that the model has high predictive performance. Some reasons for this are as follows: The model was tested with independent samples in this article, irrelevant indicators were filtered out, related indicators were included, information complementarity was realized, and the predictive performance of the model was enhanced. The difference between the value predicted by the model and the actual value through the goodness-of-fit test was not statistically significant, indicating that there was no overfitting in the model, which is suitable for clinical promotion and application. Therefore, building a model based on the various influencing factors of PPD in older pregnant women can effectively predict PPD risk, providing a new approach for medical personnel to assess high-risk populations early to develop personalized management measures. For example, strengthening psychological counseling and health education for high-risk populations, advising family members to provide material and spiritual support to new mothers, helping mothers relieve stress, guiding mothers and their families in the care of newborns, enhancing maternal feeding confidence, and reducing the incidence of depressive symptoms are some possible management measures.

However, our study still has some limitations: (1) This was a single-center study with a single source of patients, and the representativeness is relatively limited; and (2) the sample size was small, which may lead to biased results. More participants need to be included to validate the conclusion.

CONCLUSION

The risk of PPD among older pregnant women is closely related to their educational level, family relationships, pregnancy complications, and the admission of newborns to the neonatal department after birth. A PPD risk prediction model for older postpartum women with good discrimination should be constructed.

ARTICLE HIGHLIGHTS

Research background

Postpartum depression (PPD) is a mental illness that can be caused by multiple factors, including the process of physical recovery in the postpartum period, newborn health, psychological stress, *etc*. The physiological functions of older pregnant women are far inferior to those of younger women. The process of physical recovery in the postpartum period is slow, and the decrease in a mother's own physiological stress ability makes them more prone to mental and psychological disorders.

Research motivation

Exploring the influencing factors of PPD in older pregnant women and constructing predictive models will provide guidance for the clinical evaluation of PPD risk in older pregnant women and the development of relevant measures.

Research objectives

This study aimed to identify the influencing factors of PPD in older pregnant women and construct a prediction model based on the influencing factors of PPD in older pregnant women.

Research methods

This study used a cross-sectional survey to investigate the PPD status of older pregnant women in our hospital and collected their data for analysis.

Research results

The incidence of PPD in older pregnant women at 42 d postpartum was 21.34%. Among these older pregnant women, a high school education and below, poor family relationships, pregnancy complications, and the separation of the mother and baby after birth were all influencing factors for PPD. A prediction model built based on these factors had high prediction efficiency.

Research conclusions

The risk of PPD among older pregnant women is closely related to their educational level, family relationships, pregnancy complications, and the admission of newborns to the neonatal department after birth. Constructing a PPD risk prediction model for older postpartum women based on the above factors can enable medical staff to perform early assessment of PPD risk for older pregnant women.

Research perspectives

The influencing factors of PPD in older pregnant women were identified, and a predictive model was constructed based on these influencing factors to determine the risk of PPD in older pregnant women in the future.

FOOTNOTES

Author contributions: Chen L and Shi Y onceived and designed the study; Shi Y guided the study; Chen L collected the clinical date; Chen L and Shi Y analyzed the data; all authors drafted and revised the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Suzhou Ninth People's Hospital.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

Relationship between nightmare distress and depressive symptoms in Chinese emergency department nurses: A cross-sectional study

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Abstract

BACKGROUND

Most of the recent research on nightmare distress and depressive symptoms has focused on adolescents and students, with less research on the nurse population. Emergency department nurses are at high risk for nightmare distress and depressive symptoms, but no studies have been conducted to explore the relationship between the two; thus, further investigation is needed.

AIM

To understand the relationship between nightmare distress and depressive symptoms among emergency department nurses in China.

METHODS

A convenience sampling method was used to select 280 emergency department nurses from nine provinces, including Jiangxi, Sichuan, Jiangsu, and Shanxi Provinces. The Chinese version of the Nightmare Distress Questionnaire and the Center for Epidemiological Studies Depression Scale (CES-D) were administered.

RESULTS

Emergency department nurses' nightmare distress scores were positively associated with depressive symptom scores (r = 0.732), depressed affect (r = 0.727), somatic symptoms (r = 0.737), and interpersonal difficulty (r = 0.647). Further multiple linear regression analyses showed that education level, work pressure, self-reported health, and CES-D scores were factors that influenced nightmare distress among Chinese emergency department nurses ($P < 0.05$).

CONCLUSION
Nightmare distress is closely associated with depressive symptoms in Chinese emergency department nurses, and early intervention is recommended for professionals with this type of sleep disorder to reduce the occurrence of depressive symptoms.

Key Words: Nightmare distress; Emergency department nurses; Depressive symptoms; Workplace violence; Observational study; China

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Core Tip: Understanding the relationship between nightmare distress and depressive symptoms in emergency department nurses and adopting effective interventions could reduce their incidence in this population. Currently, most studies on nightmare distress and depressive symptoms have focused on adolescents or students, and fewer have examined emergency department nurses. This study is the first to examine the relationship between nightmare distress and depressive symptoms among emergency department nurses, providing a theoretical basis for developing effective interventions.

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INTRODUCTION

The International Classification of Diseases, 10th Revision[1] defines a nightmare as an extremely disturbing and memorable dream, that is, recurring dreams that involve danger to the health, survival, and dignity of the individual while he or she sleeps. Nightmares are a fearful and distressing experience; when individuals wake after a nightmare, the content of the dream is clearly recalled, and they have difficulty falling asleep[2]. Studies have shown that nightmares not only affect an individual's sleep quality, including insomnia and difficulty falling asleep[3], but are also a major risk factor for suicide, depression, and posttraumatic stress disorder[3-5]. A large sample survey showed that people with nightmare distress are more likely to have depressive symptoms than healthy groups[6]. Most of the recent studies on nightmare distress and depressive symptoms have focused on adolescents and students[2,3,6], but fewer studies have been conducted on the nurse population. Nurses are a high-risk group for nightmare distress[7], especially emergency department nurses, possibly because they often witness patient deaths and severe trauma[8]. Furthermore, due to the special nature of the work environment, these professionals are often subjected to threats, verbal violence, and even physical violence from patients and families[9,10]. Therefore, the aim of this study was to explore the relationship between nightmare distress and depressive symptoms among Chinese emergency department nurses through a cross-sectional survey and to inform interventions to improve the working environment of emergency department nurses globally and reduce the occurrence of nightmare distress and depressive symptoms in this population.

MATERIALS AND METHODS

Participants and research design

This study had a multicenter cross-sectional design. In March to April 2023, a convenience sampling method was used to select emergency nurses from tertiary hospitals in nine Chinese provinces (Jiangxi, Sichuan, Jiangsu, Shanxi, Guangdong, Hebei, Zhejiang, Hainan, and Shaanxi). The inclusion criteria were as follows: (1) Employment as an emergency department nurse; and (2) Voluntary participation in this study. The exclusion criteria for nurses were as follows: (1) On leave during the survey period; (2) Trainees; or (3) Receiving further training from the hospital. The rejection criteria were as follows: (1) Completed the questionnaire incompletely; or (2) Had answers to the questionnaire that were obviously repeated. The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (ethics number: IIT2023196).

Sample

This study collected sociodemographic data and work-related data, and a total of 19 independent variables were included. According to the calculation formula[11], the necessary sample size was 5-10 times that of the number of independent variables; considering the possibility of 20% invalid samples, a minimum of 114 participants were needed. A total of 300 questionnaires were distributed in this study; of these, 280 were finally included in the analysis after excluding invalid responses. The questionnaire return efficiency was 93.33%.

Measures

General information: Custom-designed questionnaires were based on published studies in the field[12,13] and expert opinions. The questionnaires covered mainly sociodemographic characteristics (such as sex, age, and marital status) and work-related factors (title, years of work, number of night shifts per month, work pressure, and frequency of violence in the workplace).

Nightmare distress: Nightmare distress was measured using the Chinese version of the Nightmare Distress Questionnaire (NDQ-CV)[14], which is an adaptation of the Nightmare Distress Questionnaire (NDQ)[15]. The NDQ-CV includes a total of 14 items in two dimensions: General nightmare distress and daytime reality perception. Each item is rated on a 5-point scale from 1 (never) to 5 (always), and the total score of the scale ranges from 14 to 70, with higher scores associated with higher levels of nightmare distress. The Cronbach's a coefficient for the total scale in this study was 0.942, and the Kaiser-Meyer-Olkin value was 0.951 ($P < 0.05$), indicating good reliability.

Depressive symptoms: Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D was developed by Radloff[16] and translated into Chinese by Zhang *et al*[17]. The scale includes four dimensions: Depressed affect, positive affect, somatic symptoms, and interpersonal difficulty. It has 20 items, four of which are reverse scored. Each item is rated on a scale from 0 to 3, for a total score ranging from 0 to 60. The higher the score, the more severe the depressive symptoms. A score ≥ 20 indicates significant depressive symptoms. In this study, the Cronbach's a coefficient of the total scale was 0.866, and the KMO value was 0.956 ($P < 0.05$), indicating good reliability.

Quality control

In this study, 20 emergency department nurses were randomly selected for a pilot survey in a tertiary hospital in Jiangxi Province, and the self-report questionnaire section was modified according to the problems that emerged from the pilot survey. Before the questionnaires in the formal experiment were completed, the purpose and importance of this study and the precautions for completing the questionnaires were explained by professionals, and the questionnaires were distributed after obtaining the informed consent of the study subjects. After the questionnaires were collected, the researcher reviewed the content of the completed questionnaires, and two researchers entered the data using Excel software to ensure the accuracy of the data.

Data analysis

The data were analyzed using SPSS 25.0 statistical software. Continuous data that conformed to a normal distribution are expressed as the mean ± SD, and categorical data are expressed as frequencies and percentages. Independent sample *t* tests were used to detect differences between two groups, and one-way ANOVA was used to compare multiple groups. Pearson correlation analysis was used to explore the relationship between nightmare distress and depressive symptoms; linear regression analysis was used to explore the factors influencing the emergence of nightmare distress among nurses in the emergency department. A threshold of $\alpha = 0.05$ (two-sided) was used to indicate significant differences.

RESULTS

Descriptive statistics and correlations

A total of 280 emergency department nurses (54 men and 226 women) were included in the study. Among these nurses, most were 26-35 years old (44.3%), had a bachelor's degree (76.1%), had more than 10 years of experience (39.6%), and were married (63.2%). Additionally, most of the nurses were the nurse-in-charge (37.9%), had a monthly income of 5000 to 10000 yuan (62.5%), worked 6 to 10 shifts per month (46.4%), had high pressure (44.6%), and frequently suffered from workplace violence (46.1%). Among those included, 47.5% rated their health as average, 62.5% did not regularly exercise, and the majority were from the emergency departments of Jiangxi Province (31.1%). Further details are shown in Table 1. Using nightmare distress scores as the dependent variable and sociodemographic characteristics as independent variables, comparisons were conducted. The influence of dichotomous variables (*e.g.*, sex) was tested using independent sample *t* tests, and that of variables with multiple categories (*e.g.*, education level) were examined by one-way ANOVA to compare nightmare distress scores among emergency department nurses with different characteristics. The results of the univariate analysis showed that nightmare distress scores of emergency department nurses significantly differed according to sex, education level, working years, monthly income, work pressure, self-reported health, and province ($P < 0.05$; Table 1).

Correlation of nightmare distress with depressive symptoms

Pearson correlation analysis showed that nightmare distress total score and subscale scores were positively correlated with depressive symptom total score, depressed affect, somatic symptoms, and interpersonal difficulties and negatively correlated with positive affect ($P < 0.01$), as shown in Table 2.

Multivariate regression of nightmare distress

Multiple linear regression analysis with the NDQ-CV total score as the dependent variable and sex, education level, years of work, monthly income, work pressure, self-reported health, province, and CES-D total score as the independent variables (assignments are shown in Table 3) showed that education level, work pressure, self-reported health, and CES-

Table 1 Nightmare distress scores among emergency department nurses with different characteristics

Variable	Level	*N* (%)	Score (mean ± SD)	*t*/*F*	Degrees of freedom	*P* value
Sex	Male	54 (19.3)	42.39 ± 10.83	4.828		< 0.001
	Female	226 (80.7)	34.61 ± 10.59			
Age (yr)	≤ 25	55 (19.6)	37.55 ± 12.52	0.430	3/276	0.732
	26-35	124 (44.3)	35.63 ± 11.56			
	36-45	88 (31.4)	35.78 ± 9.70			
	> 45	13 (4.6)	36.85 ± 8.36			
Educational level	Associate degree	52 (18.6)	34.12 ± 10.81	8.441	2/277	< 0.001
	Bachelor's degree	213 (76.1)	35.84 ± 10.87			
	Graduate degree or above	15 (5.4)	46.87 ± 8.90			
Marital status	Unmarried	92 (32.9)	37.13 ± 12.27	1.048	2/277	0.352
	Married	177 (63.2)	35.42 ± 10.48			
	Divorced or widowed	11 (3.9)	38.73 ± 8.87			
Years of work	< 1	10 (3.6)	33.70 ± 11.94	3.507	3/276	0.016
	1-5	98 (35.0)	38.92 ± 12.13			
	6-10	61 (21.8)	35.41 ± 11.38			
	> 10	111 (39.6)	34.23 ± 9.30			
Title	Junior nurse	44 (15.7)	33.14 ± 12.31	1.761	3/276	0.155
	Intermediate nurse	101 (36.1)	35.96 ± 11.64			
	Nurse-in-charge	106 (37.9)	36.76 ± 10.04			
	Senior nurse	29 (10.4)	38.76 ± 10.00			
Monthly income (yuan)	< 5000	55 (19.6)	34.36 ± 11.21	10.647	2/277	< 0.001
	5000-10000	175 (62.5)	34.86 ± 10.76			
	> 10000	50 (17.9)	42.42 ± 9.81			
Number of night shifts per month	0-5	69 (24.6)	36.62 ± 9.48	2.069	2/277	0.128
	6-10	130 (46.4)	37.13 ± 11.55			
	> 10	81 (28.9)	34.04 ± 11.33			
Work pressure	None	16 (5.7)	31.94 ± 8.91	4.388	3/276	0.005
	Mild	16 (5.7)	32.19 ± 10.36			
	Moderate	123 (43.9)	34.65 ± 10.31			
	Severe	125 (44.6)	38.58 ± 11.63			
Violence in the workplace	Never	6 (2.1)	34.33 ± 11.99	0.213	3/276	0.887
	Rarely	31 (11.1)	35.06 ± 11.97			
	Sometimes	129 (46.1)	36.03 ± 11.55			
	Always	114 (40.7)	36.58 ± 10.27			
Self-reported health	Poor	110 (39.3)	38.75 ± 11.62	5.517	2/277	0.004
	Average	133 (47.5)	34.65 ± 10.25			
	Good	37 (13.2)	33.49 ± 10.82			
Regular exercise	Yes	105 (37.5)	36.90 ± 9.91	0.920		0.359
	No	175 (62.5)	35.64 ± 11.69			
Province	Jiangxi	87 (31.1)	34.30 ± 10.97	8.835	8/271	< 0.001
	Sichuan	51 (18.2)	31.04 ± 9.48			

	Jiangsu	41 (14.6)	33.05 ± 9.24
	Shanxi	24 (8.6)	33.42 ± 7.10
	Guangdong	12 (4.3)	43.00 ± 9.10
	Shaanxi	15 (5.4)	45.93 ± 10.22
	Hainan	19 (6.8)	43.11 ± 10.79
	Zhejiang	15 (5.4)	45.07 ± 7.49
	Hebei	16 (5.7)	42.94 ± 12.54

Table 2 Correlation between nightmare distress and depression symptoms among emergency department nurses

Item	NDQ-CV total score	General nightmare distress	Daytime reality perception	CES-D total score	Depressed affect	Somatic symptoms	Interpersonal difficulties	Positive affect
NDQ-CV total score	1							
General nightmare distress	0.983[a]	1						
Daytime reality perception	0.920[a]	0.831[a]	1					
CES-D total score	0.732[a]	0.722[a]	0.667[a]	1				
Depressed affect	0.727[a]	0.713[a]	0.673[a]	0.929[a]	1			
Somatic symptoms	0.737[a]	0.713[a]	0.701[a]	0.933[a]	0.864[a]	1		
Interpersonal difficulties	0.647[a]	0.628[a]	0.612[a]	0.828[a]	0.792[a]	0.770[a]	1	
Positive affect	-0.406[a]	-0.365[a]	-0.447[a]	-0.292[a]	-0.546[a]	-0.452[a]	-0.460[a]	1

[a]$P < 0.001$.

NDQ-CV: Chinese version of the Nightmare Distress Questionnaire; CES-D: Center for Epidemiological Studies Depression Scale.

Table 3 Independent variables in multivariate regression analysis

Independent variable	Code
Gender	Male = 1, female = 2
Education level	Associate degree = 1, bachelor's degree = 2, graduate degree or above = 3
Years of work	< 1 year = 1, 1-5 years = 2, 6-10 years = 3, > 10 years = 4
Monthly income	< 5000 = 1, 5000-10000 = 2, > 10000 = 3
Work pressure	None = 1, mild = 2, moderate = 3, severe = 4
Self-reported health	Poor = 1, average = 2, good = 3
Province	Jiangxi = 1, Sichuan = 2, Jiangsu = 3, Shanxi = 4, Guangdong = 5, Shaanxi = 6, Hainan = 7, Zhejiang = 8, Hebei = 9

D scores were the factors influencing nightmare distress among emergency department nurses ($P < 0.05$; Table 4).

DISCUSSION

The results of this study showed a positive correlation between nightmare distress scores and depressive symptom scores, indicating that higher levels of nightmare distress among emergency department nurses are associated with more severe depressive symptoms, which is consistent with the results of previous studies[2,3,18]. Studies have shown that the amygdala, medial prefrontal cortex, hippocampus, and anterior cingulate cortex differ between patients with nightmare

Table 4 Multiple linear regression analysis results regarding nightmare distress in emergency department nurses

Item	*b*	SE	*β*	*t*	*P* value
Education level	2.051	0.982	0.088	2.088	0.038
Working pressure	1.154	0.543	0.085	2.124	0.035
Self-reported health	-1.338	0.649	-0.082	-2.064	0.040
CES-D total score	0.782	0.053	0.641	14.741	< 0.001

R2 = 0.570, adjusted *R2* = 0.557; CES-D: Center for Epidemiological Studies Depression Scale.

distress and healthy individuals[18,19]. Among these areas, the amygdala is the main area involved in negative emotions such as fear and depression and is the central part responsible for emotions; the anterior cingulate cortex plays a major role in regulating emotions and selective attention; and the hippocampus is the main area supporting memory. The anterior cingulate cortex, prefrontal cortex, and amygdala exhibit high activity in patients with nightmare distress, while the hippocampus is biased toward remembering negative emotions, increasing the risk of depressive symptoms[19]. Chen and Li[20] showed that the hypothalamic-pituitary-adrenocortical axis exhibits abnormal activation in patients with nightmare distress, with altered levels of cortisol and melatonin. Changes in the circadian rhythm of melatonin secretion are closely associated with a variety of alterations in individuals; disruption of melatonin homeostasis (lower melatonin levels) is a pathological basis for the induced symptoms of depression in patients. Mahar *et al*[21] showed that chronic stress leads to attenuation of cell proliferation and neurogenesis, phosphorylation of extracellular signal-regulated kinase, substantial attenuation of 5-hydroxytryptamine (5-HT) levels and 5-HT auto-receptor sensitivity, and reduction of hippocampal inhibition of the hypothalamus-pituitary-adrenal axis, which induces depressive symptoms in nightmare-plagued patients. In addition, sleep disorders caused by nightmare disturbances lead to an abnormal increase in inflammatory factors and impairment of autophagy. Li *et al*[22] showed that the levels of inflammatory factors such as NLRP1, tumor necrosis factor-α, and interleukin-1β in the hippocampus of sleep-disturbed mice were markedly increased, and the levels of the autophagy proteins Atg5 and Atg7 were significantly reduced, thus inducing neuroinflammation and consequently depressive symptoms. Levin and Nielsen[23] showed that patients with nightmare distress are more likely to have neurotic, stress-related symptoms and that patients with high levels of nightmare distress have stronger memories of their nightmares because they recollect the dream content during waking hours as a coping mechanism, thus increasing their risk of developing depressive symptoms[18].

In the present study, multiple regression analysis showed that education level, work pressure, self-reported health, and depressive symptoms are independent factors that influence nightmare distress among emergency department nurses. The higher the education level and work pressure, the higher the nightmare distress score of emergency department nurses, possibly because a higher education level is associated with higher self-esteem and higher levels of perceived stress, which in turn increase the risk of nightmare distress[2,24]. Emergency department nurses with poorer self-reported health have lower immunity, and sleep quality decreases when they are overworked, resulting in shorter bouts of deep sleep and increased time in light sleep stages, which are more susceptible to external stimuli, leading to insomnia and nightmare distress[25]. Studies have shown that patients with depressive symptoms have altered sleep structure and significantly impaired sleep quality[25]; impaired sleep is an important factor contributing to nightmare distress. In addition, patients with depressive symptoms exhibit long-term states of sadness and uneasiness, which affects the normal regulatory function of the cerebral cortex, thus increasing the risk of nightmare distress[3]. Therefore, it is recommended that hospital administrators should optimize the management of the emergency department, conduct regular psychological symposiums to alleviate the workplace pressure of emergency department nurses, and provide emergency department nurses with spiritual and material support to bolster their sense of professional identity. Emergency department nurses themselves should increase their exercise levels and improve physical health; those with more severe nightmare distress and depressive symptoms should seek psychotherapy treatment, such as cognitive-behavioral therapy [26], imagery rescripting, and imaginal exposure[27], to improve their mental health and psychological resilience, alleviate nightmare distress and depressive symptoms, and improve their quality of life.

Strengths and limitations

This study has several strengths. First, the sample consisted of emergency department nurses from multiple provinces, and the findings have strong generalizability. Second, this is the first study to explore the relationship between nightmare distress and depressive symptoms among Chinese emergency department nurses; our findings can inform intervention guidelines for reducing nightmare distress and depressive symptoms among emergency department nurses and even other nurses worldwide. Finally, this study adopted an anonymous survey method, which was conducive to obtaining real information about the participants and improved the reliability of its results.

Likewise, this study has some limitations. First, this was a cross-sectional study that only explored the correlation between nightmare distress and depressive symptoms among emergency department nurses; future longitudinal studies are needed to elucidate the causal relationship between the two variables. Second, the assessment instruments used were all self-report questionnaires. Self-report data are highly subjective and may contain information bias, and future studies are needed to verify the relationship between nightmare distress and depressive symptoms among emergency department nurses in conjunction with more specialized diagnostic methods. Finally, emergency department nurses were

selected from only one hospital in some provinces included this study, which may lead to selection bias, and larger sample sizes should be used in future research.

CONCLUSION

This study analyzed the relationship between nightmare distress and depressive symptoms among Chinese emergency department nurses and concluded that nightmare distress and depressive symptoms were positively correlated among these professionals. The results of the current analysis showed that emergency department nurses' nightmare distress was influenced by a variety of factors. In the future, researchers should conduct randomized controlled studies of the relationship between nightmare distress and depressive symptoms among emergency department nurses and explore related interventions to reduce the severity of nightmare distress and depressive symptoms among emergency department nurses.

ARTICLE HIGHLIGHTS

Research background

Emergency department nurses are at high risk for nightmare distress and depressive symptoms. Understanding the relationship between nightmare distress and depressive symptoms and adopting appropriate interventions can alleviate nightmare distress and depressive symptoms among emergency department nurses. Therefore, this study was conducted to explore the correlation between nightmare distress and depressive symptoms among emergency department nurses through a cross-sectional survey.

Research motivation

Mental health issues are increasingly pronounced among emergency department nurses. This study aimed to elucidate the relationship between nightmare distress and depressive symptoms among emergency department nurses and to suggest effective interventions to improve their mental health.

Research objectives

This study investigated emergency department nurses in several provinces in China to explore the relationship between nightmare distress and depressive symptoms in this population.

Research methods

In this study, 280 emergency department nurses in nine provinces were selected using a convenience sampling method. They completed the Chinese version of the Nightmare Distress Questionnaire and the Center for Epidemiological Studies Depression Scale. SPSS 25.0 statistical software was used to analyze the collected data.

Research results

The results of this study showed that more severe nightmare distress among emergency department nurses was associated with more pronounced depressive symptoms and that the severity of nightmare distress in this population was influenced by factors such as education level, work stress, and self-reported health.

Research conclusions

The severity of nightmare distress in emergency department nurses is positively correlated with depressive symptoms. Nightmare distress can cause serious psychological problems, and early interventions for this population can alleviate depressive symptoms. This study provides a theoretical basis for developing effective interventions.

Research perspectives

This study investigated emergency department nurses in only China; future studies could include those in multiple countries to achieve a comprehensive understanding of the relationship between nightmare distress and depressive symptoms among emergency department nurses and to promote mental health in this profession.

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FOOTNOTES

Author contributions: Gan QW conceived, researched, analyzed, and wrote this manuscript; Yu R was responsible for conceptualization, research design, and data protection; Lian ZR provided methodological guidance and data analysis; Zheng LL revised the manuscript and oversaw quality control; Yuan YL and Li YP conducted the investigations and data collection.

Institutional review board statement: The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (Ethics number: IIT2023196).

Informed consent statement: The study was conducted in strict compliance with the Declaration of Helsinki, and all subjects who participated in the study were informed of the study and agreed to complete the questionnaire.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data for this study can be provided with the consent of the first author and corresponding author.

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ORIGINAL ARTICLE

Observational Study

Mediating role of physical activity in the relationship between psychological distress and intimate relationships among stroke patients

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Abstract

BACKGROUND

Stroke patients often experience psychological distress, which can impact their intimate relationships with spouses, subsequently influencing their treatment and recovery. Physical activity is considered a key rehabilitation method for stroke patients. This paper aims to analyze whether psychological distress affects intimate relationship between spouses through physical activity.

AIM

To explore the mediating effect of physical activity between psychological distress and intimate relationship in stroke patients.

METHODS

A total of 256 stroke patients who underwent treatment at the First People's Hospital of Shangqiu between July 2021 and July 2022 were enrolled in this study. The participants completed questionnaires, including the Kessler Psychological Distress Scale (K10), the Quality of Relationship Index (QRI), International Physical Activity Questionnaire, and a general information questionnaire. Data analysis were performed using SPSS 23.0. The Harman test was employed to detect common method deviations, and Spearman correlation was used for correlation analysis. The mediating effect was assessed using Process 3.4.1, with significance testing of the regression coefficients conducted using the bias-corrected percentile Bootstrap method (5000 iterations, 95% confidence interval). Statistical significance was set at $P < 0.05$.

RESULTS

The results showed that patients scored an average of 21.61 ± 6.44 points on the K10, 32.40 ± 6.19 points on the QRI; the median physical activity level according to the International Physical Activity Questionnaire was 1861 (566, 2846)

MET·min/w. The level of physical activity (the physical activity intensity of the patients reflected by the International Physical Activity Questionnaire-Long Form scale) negatively correlated with psychological distress and intimacy ($P < 0.05$), and positively correlated with each other ($P < 0.05$), with the correlation stronger at lower physical activity levels compared to higher ones. The mediating effect of physical activity between psychological distress and intimate relationship was calculated to be 40.23%. Bootstrap analysis further validated the results. The mediating effect of psychological distress on intimate relationships through physical activity level was -0.284, with a confidence interval of -0.409 to -0.163, excluding 0, confirming a significant mediating effect of psychological distress on intimate relationships.

CONCLUSION

Physical activity significantly affects relationship between psychological distress and intimate relationships among stroke patients. Addressing the role of physical activity may have implications for improving patient outcomes and rehabilitation strategies.

Key Words: Stroke; Cross-sectional study; Psychological distress; Intimate relationship; Mediating effect; Physical activity level

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Core Tip: Psychological distress is prevalent among stroke patients and can significantly impact their intimate relationships with spouses. Physical activity plays a crucial role in stroke prevention and rehabilitation. This study successfully identified a mediating effect of physical activity on psychological distress and intimate relationships, among stroke patients, confirmed through the Bootstrap test. These findings provide a robust foundation for promoting stroke patient rehabilitation and addressing relationship challenges between spouses.

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INTRODUCTION

Stroke is not simply a singular disease; rather, it encompasses a group of conditions resulting from impaired brain function caused by cerebrovascular disease[1]. With its high incidence, disability, mortality and recurrence rate, stroke has become a global health concern, leading to numerous disabilities and deaths in China[2]. During the post-stroke treatment and rehabilitation process, patients often face stigma and significant psychological distress due to disabilities and disruptions in their self-image[3]. Intimate relationships, characterized by communication that fosters intimacy and cooperation within an interdependent framework, play a crucial role in the lives of stroke patients and their spouses[4]. Spouses of stroke patients endure long-term care and economic burdens and experience multiple psychological pressures from family and society, which can negatively impact their relationship and mutual happiness[5]. Research indicates that regular physical activity is a vital preventive measure against stroke, attributed to its potential to improve vascular function and reduce stroke-related risk factors[6]. Therefore, physical activity can potentially aid patient rehabilitation, delay deterioration of their condition, alleviate psychological distress, and mitigate the adverse effects of negative emotions on the relationship between stroke patients and their spouses. However, there is a lack of research on the interplay among physical activity level, psychological distress, and intimacy in the context of stroke patients, both domestically and globally. Therefore, this study aimed to investigate whether the level of physical activity acts as a mediating factor between psychological distress and intimacy in stroke patients. By exploring this relationship, the study seeks to provide novel insights into alleviating the strains within the spousal relationships among stroke patients.

MATERIALS AND METHODS

Patient characteristics

This cross-sectional survey involved 256 patients who received stroke-related treatment at the First People's Hospital of Shangqiu between July 2021 and July 2022. Inclusion criteria were as follows: (1) Patients meeting the diagnostic criteria of stroke and diagnosed with stroke through head computed tomography or magnetic resonance imaging; (2) Age under 80 years; (3) Married and cohabitating with a spouse; and (4) Stable condition, clear consciousness, and no obvious language comprehension and expression disorders. Exclusion criteria included: Severe heart, liver or kidney dysfunction, respiratory failure and malignant tumors. The study received ethical approval from the First People's Hospital of

Shangqiu (2021-125-29), and all participants provided informed consent voluntarily.

Research tools

Figure 1 illustrates the study process. The following research tools were utilized: (1) General information questionnaire: A self-designed questionnaire capturing demographic data (*e.g.*, age, gender) and disease-related information (*e.g.*, stroke attack, stroke course); (2) The Kessler Psychological Distress Scale (K10)[7]: Used to assess the mental health status of individuals, comprising ten items scored on a five-level scale (score range: 10-50). Higher scores indicate poorer mental health status (Cronbach's α = 0.896); (3) The Quality of Relationship Index (QRI)[8]: Evaluates satisfaction with intimate relationships using six items rated on a 7-level scale (score range: 6-42). Higher scores indicate higher satisfaction with intimate relationships (Cronbach's α = 0.943); and (4) International Physical Activity Questionnaire-Long Form (IPAQL)[9]: Measures patients' health-related physical activity over the past week and calculates metabolic equivalents. The questionnaire covers physical activities (work-related, transportation, daily life, sports, and leisure), sedentary behavior, and sleep. Among them, four types of physical activities were evaluated for walking, moderate and severe physical activities, with a total of 27 items. The total metabolic equivalent was used to evaluate the overall physical activity level. Higher scores indicate better physical activity levels (Cronbach α = 0.827). For analysis, the total metabolic equivalent scores were sorted from small to large, and the first 50% and the last 50% were divided into two groups: Lower activity group and higher activity group.

Quality control

A sample size of 256 patients was deemed sufficient, meeting the requirement of seven times the number of research variables (based on the largest number of items in the International Physical Activity Questionnaire, 27 items) with a consideration of a 20% missing rate. The investigators, designated by the hospital, distributed and collected the questionnaires on-site with unified guidance. If respondents were unable to complete the questionnaire themselves, investigators assisted them in filling it out based on the their inputs. Missing items were addressed promptly to ensure complete and accurate information was obtained. Double entry and verification of data were conducted to ensure the validity, accuracy and integrity of data entry.

Statistical analysis

Data processing was performed using SPSS 23.0 (IBM Corp., Armonk, N.Y., United States). Normally distributed measurement data are presented as mean ± SD, while skewed distribution data are expressed as median (M) and quartile (P_{25}, P_{75}). Count data are expressed as cases (%). The Harman single factor test was used to test for common method bias. Spearman correlation analysis was used for correlation analysis. The mediating effect was tested by Process 3.4.1 (Designed by Andrew F. Hayes based on SPSS), and the significance of regression coefficients was assessed using the bias-corrected percentile Bootstrap method (5000 iterations, 95% confidence interval). Statistical significance was set at $P < 0.05$.

RESULTS

Clinical characteristics

A total of 260 questionnaires were distributed, and 256 valid questionnaires were collected, yielding an effective response rate of 98.46%. Among the participants, 195 were male (76.17%) and 61 were female (23.83%). The age distribution was as follows: 28 patients (10.94%) were younger than 45 years, 132 patients (51.56%) were between 45 and 60 years, and 96 patients (37.50%) were older than 60 years. The proportion of patients with junior high school education was the largest (40.23%), and the college or higher had the lowest proportion (14.84%). More than ninety percent of the patients had a year of marriage of more than 20 years (92.19%), and only 7.81% (20/256) of the patients had less than 20 years. There are 71.88% (184/256) of the patients were a first-ever stroke. The type of stroke in 3.52% (9/256) of patients were hemorrhagic, 94.14% (241/256) were ischemic, and 2.34% (6/256) were hybrid. About 7 percent of the patients had self-care ability and did not need to rely on others for activities, 65.24 % of the patients had mild dependence, and 27.73 % of the patients had moderate and heavy dependence (Table 1).

Common method bias

To address potential common method bias, quality control measures were implemented during the investigation. Factor analysis of the questionnaires was conducted, and the Harman test showed that the eigenvalue of two factors exceeded 1, accounting for a maximum of 34.59% (< 40%), indicating no significant common method deviation.

Comparison of K10 and QRI scores

The study found that the average K10 score of the 256 patients was 21.61 ± 6.44 points, while the average QRI score was 32.40 ± 6.19 points. Significant differences in K10 and QRI scores were observed among patients with different physical activity levels ($P < 0.05$) (Figure 2).

Correlation analysis

Correlation analysis was performed among psychological distress (K10), intimate relationship (QRI), and metabolic equivalent (IPAQL) in patients with different physical activity levels. In the lower activity group, psychological distress

Table 1 General characteristics of the stroke patients

Clinical features	Cases	Constituent ratio (%)
Sex		
Male	195	76.17
Female	61	23.83
Age (yr)		
< 45	28	10.94
45-60	132	51.56
> 60	96	37.50
BMI (kg/m^2)		
< 18.5	6	2.34
18.5-23.9	71	27.73
24-27.9	84	32.81
≥ 28	95	37.12
Educational		
Primary school or below	73	28.52
Junior high school	103	40.23
Senior high school	42	16.41
College or higher	38	14.84
Personal monthly income (Yuan)		
< 1000	68	26.56
1000-3000	61	23.83
3001-5000	69	26.95
> 5000	58	22.66
Payment method		
Medical insurance	219	85.55
Private expense	37	14.45
Year of marriage (yr)		
< 10	9	3.51
10-20	11	4.30
> 20	236	92.19
Frequency		
First	184	71.88
Recurrence	72	28.12
Course (mo)		
< 6	193	75.39
6-12	5	1.95
13-36	12	4.69
> 36	46	17.97
Type		
Hemorrhagic	9	3.52
Ischemic	241	94.14
Hybrid	6	2.34

Staging		
Acute stage	215	83.98
Recovery stage	23	8.98
Sequelae stage	18	7.04
Dysfunction		
No	223	87.11
Yes	33	12.89
Long-term medication history		
No	121	47.27
Yes	135	52.73
Combined types of chronic diseases (type)		
0	89	34.77
1	117	45.70
2	43	16.80
≥ 3	7	2.73
Self-care ability		
Heavy dependence	5	1.95
Moderate dependence	66	25.78
Mild dependence	167	65.24
No need to rely on	18	7.03

exhibited negative correlations with intimacy and metabolic equivalent (r = -0.523, P < 0.001; r = -0.528, P < 0.001), while intimate relationship positively correlated with metabolic equivalent (r = 0.631, P < 0.001). In the higher activity group, psychological distress showed negative correlations with intimate relationship and metabolic equivalent (r = -0.481, P < 0.001; r = -0.265, P < 0.001), and a positive correlation between intimate relationship and metabolic equivalent (r = 0.476, P < 0.001) was observed (Figure 3).

Mesomeric effect

The mediating effect analysis revealed that psychological distress significantly influenced intimate relationships in the first step (b = -0.734, P < 0.001), indicating a total effect. In the second step, psychological distress had a significant effect on physical activity level (b = -0.650, P < 0.001). In the third step, both psychological distress and physical activity level significantly affected intimate relationships (b = -0.439, P < 0.001; b = 0.454, P < 0.001), establishing a partially mediated model through activity level (Table 2).

The results were further validated through Bootstrap analysis. It was found that: (1) The total effect of psychological distress on intimate relationships was -0.706, with a confidence interval of -0.786 to -0.625, indicating a significant total effect; (2) The direct effect of psychological distress on intimate relationships was -0.422, with a confidence interval of -0.514 to -0.330 also signifying a significant direct effect; and (3) The mediating effect of psychological distress on intimate relationships through physical activity level was -0.284, with a confidence interval of -0.409 to -0.163, excluding 0, confirming a significant mediating effect of psychological distress on intimate relationships (Table 3).

The level of physical activity was found to act as a mediating factor between psychological distress and intimacy, and the mediating model was established. The psychological distress-physical activity level-intimacy relationship exhibited a partial mediating effect, accounting for 40.23% of the total effect (Figure 4).

DISCUSSION

Stroke patients often experience language impairment and motor dysfunction, leading to reduced self-care ability and social adaptability, which can result in psychological distress for both the patients and their partners[10]. As the main caregivers in the family, partners' attitudes and caregiving abilities directly influence the patient's mood and rehabilitation progress[11]. Importantly, alleviating psychological distress can enhance the relationship between patients and partners, foster open communication, and improve marital happiness and overall quality of life for spouses[12]. Previous studies have identified hypertension, diabetes, dyslipidemia, and obesity as risk factors associated with stroke, and physical activity can have a positive impact on these risk factors[13,14]. Physical activity can positively impact these risk factors by improving vasodilation, reducing diabetes, hypertension, dyslipidemia, obesity, and depression risk, thus

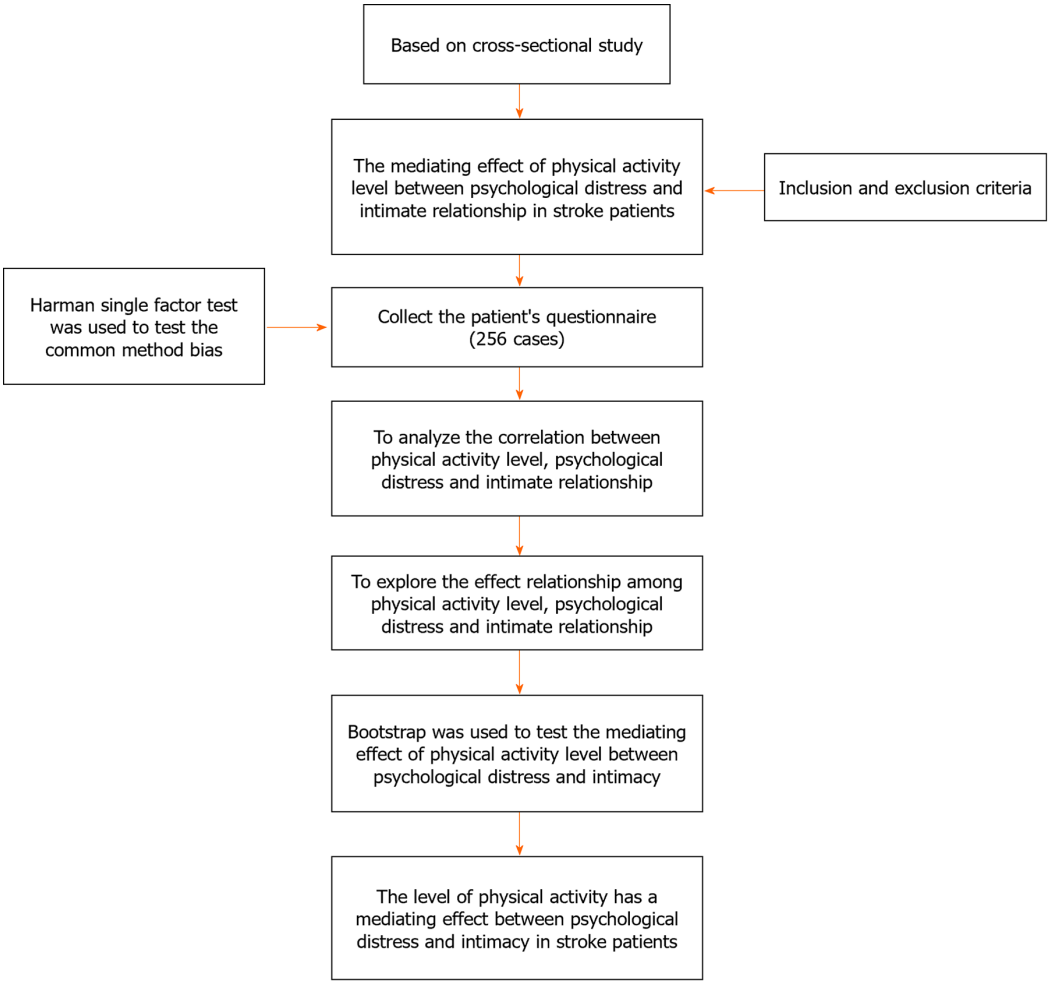
Table 2 Process method to test the mediating effect

Procedure	Dependent variable	Independent variable	R^2	β	*F* value	*t* value	*P* value
Step one	Intimate relationship	Psychological distress	0.536	-0.734	296.150	-17.209	< 0.001
Step two	Physical activity	Psychological distress	0.420	-0.650	185.574	-13.623	< 0.001
Step three	Intimate relationship	Psychological distress	0.655	-0.439	242.710	-9.063	< 0.001
		Physical activity		0.454		9.377	< 0.001

Table 3 Bootstrap analysis of the mediating effect

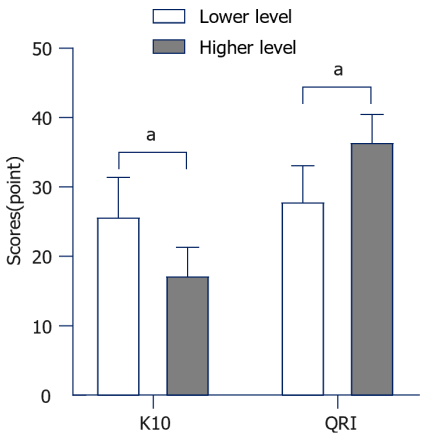
Index	Effect	SE	*t* value	*P* value	95%CI
Direct effect	-0.422	0.047	-9.062	< 0.001	-0.514 to -0.330
Indirect effect	-0.284	0.064	-	-	-0.409 to -0.163
Total effect	-0.706	0.041	-17.209	< 0.001	-0.786 to -0.625

CI: Confidence interval.



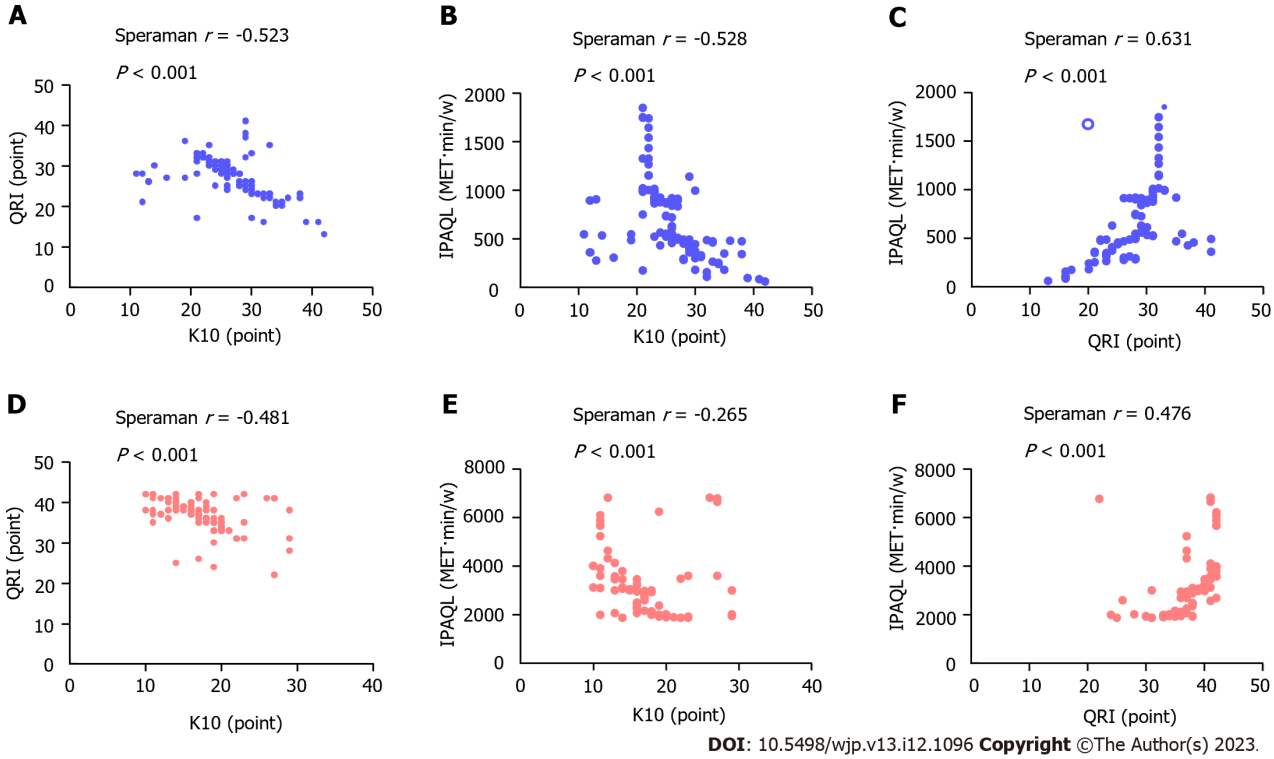
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Figure 1 Flowchart providing the steps and approach of this study.



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Figure 2 The Kessler Psychological Distress Scale and Quality of Relationship Index scores of stroke patients based on physical activity level. $^{a}P < 0.05$. QRI: The Quality of Relationship Index; K10: The Kessler Psychological Distress Scale.

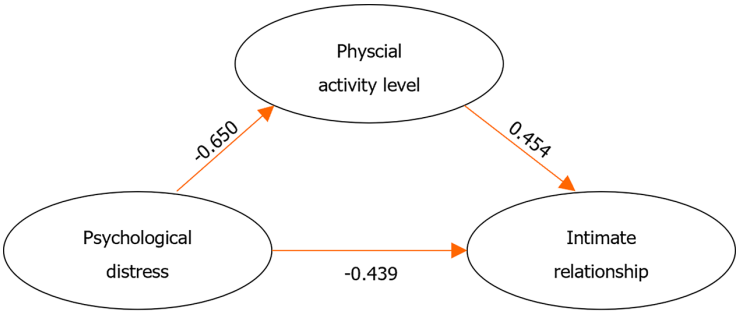


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Figure 3 Correlation analysis of patients' psychological distress, intimate relationship satisfaction, and physical activity level. A: Lower activity level group, the correlation between psychological distress [the Kessler Psychological Distress Scale (K10)] and intimate relationship satisfaction [the Quality of Relationship Index (QRI)]; B: Lower activity level group, the correlation between psychological distress (K10) and physical activity level [International Physical Activity Questionnaire-Long Form (IPAQL)]; C: Lower activity level group, the correlation between intimate relationship satisfaction (QRI) and physical activity level (IPAQL); D: Higher activity level group, the correlation between psychological distress (K10) and intimate relationship satisfaction (QRI); E: Higher activity level group, the correlation between psychological distress (K10) and physical activity level (IPAQL); F: Higher activity level group, the correlation between intimate relationship satisfaction (QRI) and physical activity level (IPAQL). K10: The Kessler Psychological Distress Scale; QRI: The Quality of Relationship Index; IPAQL: International Physical Activity Questionnaire-Long Form.

promoting stroke recovery and delaying deterioration. Therefore, moderate physical activity can aid stroke patients' recovery, reduce their psychological distress, and help restore and improve the relationship between patients and their partners.

The prevalence of psychological distress among stroke patients in China is high, with post-stroke depression and anxiety reported at 84.51% and 75.63%, respectively[15]. Psychological distress significantly hampers treatment, rehabilitation, long-term function, and quality of life for stroke patients, increasing the risk of stroke recurrence and mortality [16]. Physical activity refers to bodily movements that requires energy expenditure, primarily achieved through skeletal muscle contraction. It encompasses both structured and physical exercises as well as daily activity[17]. After illness,



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Figure 4 Patient physical activity mediation model.

patients may have reduced self-care ability and fear of exercise, leading to low physical activity levels. In this study, patients with lower physical activity levels had higher scores for psychological distress (K10) and a lower scores for intimate relationship satisfaction (QRI), consistent with previous research findings[18-20]. Unimproved conditions, poor prognosis, and uncertainty about the illness cause psychological problems that lead to patient self-closure and reluctance to express thoughts and feelings to their partners, affecting the intimate relationship between them. Correlation analysis revealed significant associations among psychological distress (K10), intimate relationship satisfaction (QRI), and physical activity levels (IPAQL) in patients with different physical activity levels. Patients with lower physical activity levels showed stronger correlations, suggesting that lower physical activity levels were associated with more distress and reduced communication with spouses, leading to a greater impact on intimate relationships. Unpleasant emotional experiences can disrupt the maintenance of intimate relationships between spouses.

The mediating effect analysis indicated that physical activity levels significantly mediated the relationship between psychological distress and intimate relationship satisfaction, accounting for 40.23% of the total effect. This suggests that physical activity can alleviate the patients' psychological distress and indirectly influence the intimate relationship with their spouses. Several studies have highlighted the correlation between psychological distress and physical activity level [21]. Prolonged exposure to severe and complex stress, exceeding an individual's coping abilities, can not only affect the patient's emotional responding, but also impact their partner's well-being and marital satisfaction. Increasing physical activity, such as participating in sports, can help reduce the risk of adverse psychological states, anxiety and depression during such challenging times. In fact, stroke patients often use physical activity as part of their rehabilitation treatment. This approach can stimulate nerve and limb function recovery, regulate the sympathetic nervous system to alleviate anxiety and depression levels, enhance physical functionality, decrease disability rates, and improve daily living activities [22]. However, it is important to note that in this study, physical activity level represents only one of the mediating factors between psychological distress and intimate relationship satisfaction. This implies that physical activity plays a partial role in mediating these factors. To effectively address patients' psychological distress, a comprehensive consideration of other contributing factors is necessary. Medical professionals play a crucial role in supporting patients during their treatment journey. Encouraging patients to manage their illness correctly, guiding them and their spouses to adopt positive behaviors, and fostering effective coping strategies are essential steps to alleviate psychological distress. Furthermore, enhancing patient cooperation and strengthening the intimacy between spouses can help mitigate both the psychological and physical burdens faced by the couple.

CONCLUSION

In summary, patients' psychological distress significantly affects their intimate relationship with their spouses, and the level of physical activity serves as a crucial factor between psychological distress and intimate relationship satisfaction. Therefore, it is imperative to focus on improving patients' physical activity levels to reduce psychological distress pressure, enhance communication between spouses, and provide mutual support to foster a stronger sense of intimacy and well-being.

ARTICLE HIGHLIGHTS

Research background

The psychological distress experienced by stroke patients can significantly impact their intimate relationships with their partners.

Research motivation

The strain in spousal relationships can further exacerbate the psychological distress of stroke patients and imped their recovery process.

Research objectives
This study aims to investigate whether the level of physical activity in stroke patients influences their psychological distress and subsequently affects the quality of their intimate relationships with their spouses.

Research methods
Data was collected through questionnaires, and the presence of common method bias was verified using Harman test. The mediating effect analysis was conducted to explore the relationships between psychological distress, intimacy, and physical activity levels. The significance of the regression coefficient was verified using Bootstrap.

Research results
The findings indicate that the physical activity level of stroke patients has an impact on their psychological distress, which, in turn, influences the quality of their intimate relationships with their partners.

Research conclusions
This study has shed light on the interplay between psychological distress, intimate relationships, and physical activity levels among stroke patients, offering new insights to improve the bond between couples in such situations.

Research perspectives
As a single-center study, this research has certain limitations, and other factors may also influence the outcomes. To enhance the generalizability and validity of the findings, further expansion and external validation are warranted.

FOOTNOTES

Author contributions: Luo CY, Shen L, and Sun YM designed this study; Jiao P organized the literature; Luo CY wrote the manuscript; Tu SM reviewed the manuscript.

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ORIGINAL ARTICLE

Observational Study

Surviving the shift: College student satisfaction with emergency online learning during COVID-19 pandemic

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) epidemic disrupted education systems by forcing systems to shift to emergency online leaning. Online learning satisfaction affects academic achievement. Many factors affect online learning satisfaction. However there is little study focused on personal characteristics, mental status, and coping style when college students participated in emergency online courses.

AIM

To assess factors related to satisfaction with emergency online learning among college students in Hebei province during the COVID-19 pandemic.

METHODS

We conducted a cross-sectional survey of 1600 college students. The collected information included demographics, psychological aspects of emergent public health events, and coping style. Single factor, correlation, and multiple linear

regression analyses were performed to identify factors that affected online learning satisfaction.

RESULTS

Descriptive findings indicated that 62.9% (994/1580) of students were satisfied with online learning. Factors that had significant positive effects on online learning satisfaction were online learning at scheduled times, strong exercise intensity, good health, regular schedule, focusing on the epidemic less than one hour a day, and maintaining emotional stability. Positive coping styles were protective factors of online learning satisfaction. Risk factors for poor satisfaction were depression, neurasthenia, and negative coping style.

CONCLUSION

College students with different personal characteristics, mental status, and coping style exhibited different degrees of online learning satisfaction. Our findings provide reference for educators, psychologists, and school administrators to conduct health education intervention of college students during emergency online learning.

Key Words: COVID-19; Emergency online leaning; Online learning satisfaction; College students; Mental status; Coping style; Distance education; Psychiatric status

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Core Tip: We evaluated satisfaction with online learning and its associated factors, specifically demographic variables, mental status, and coping style of Chinese college students who participated in emergency online courses during the coronavirus disease 2019 pandemic. Little study has been focused on online acceptance of education. Our findings provide reference for educators, psychologists, and school administrators to conduct health education intervention.

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INTRODUCTION

The SARS-CoV-2 [hereafter referred to as coronavirus disease 2019 (COVID-19)] pandemic disrupted the educational, economic, and social systems of many countries[1]. To reduce the spread of the virus, countries adopted diverse control strategies such as lockdown and social distancing. COVID-19 hampered education by disrupting student learning goals in many disciplines[2]. The Chinese Ministry of Education suggested "suspending classes without suspending learning". Students across the nation were required to stay at home, and emergency online learning was widely practiced in February 2020[3]. College students urgently turned to distance education to minimize the pandemic's negative impacts on health[4]. Teachers and students were suddenly thrust into an unplanned, unwanted, uncharted, online learning experiment during COVID-19-mandated confinement. This transition increased workload, altered curricula, and eliminated hands-on experiences. In online education, students had to act more autonomously and take more responsibility for their learning[5]. Students from various backgrounds and places were required to adapt to new environmental, technological, and psychological learning conditions that may have affected academics[4,6,7]. The COVID-19 pandemic impacted a cascade of detrimental effects on college student academic performance[8]. Online learning may have been an approach to ensure student knowledge and practice in this special period, although consideration of student satisfaction is mandatory to improve academics[9].

Learning satisfaction reflects how students view their learning experiences, a crucial indicator of online learning effectiveness that is related to academic achievement[10]. The effect of online learning quality on student performance was strongly mediated by satisfaction with online learning, and ensuring student satisfaction can increase the academic success of both the institution and the student[11]. Surveys of online learning satisfaction during the COVID-19 pandemic show conflicting results. Yekefallah *et al*[10] reported that 59% of college students had poor satisfaction with online learning. Arain *et al*[12] found that the level of satisfaction was only 30% among medical students. Wilhelm *et al*[13] found that undergraduate students reported lower levels of learning, engagement, and confidence with the course materials during remote teaching compared with the face-to-face portion of the class. Conversely, Eansor *et al*[14] showed that online learning had high satisfaction levels, and student knowledge scores and self-confidence were raised because of rich online educational resources and the ability to support asynchronous and synchronous communication between students and teachers and between the students themselves[15]. These differing findings make it necessary to clarify satisfaction with online learning and factors that affect satisfaction to provide effective and targeted interventions for academics and mental and physical health.

Student factors, instructor performance, system quality, and course evaluations all affect online learning satisfaction. Mohammed *et al*[16] found that student factors and system quality were the main elements that influenced student satisfaction. Online learning satisfaction during the COVID-19 lockdown has been assessed by self-efficacy and teacher attitude towards technology integration[17], the interaction between learners and content and lecturers and learners[18], higher education teacher emotional experiences[19], internet connectivity[20], curriculum arrangement[16], and learning environment[21]. Furthermore, the COVID-19 pandemic and related restrictions could impact mental health; college students and young adults had a high prevalence of anxiety, depression, sleep problems, and suicidal ideation[22]. Ionescu *et al*[23] reported that the higher the psychopathology scores, the less online learning satisfaction. Self-directed learning was negatively associated with negative emotions[24]. In addition, University period is a critical time for shaping a student's personality and developing talents; college students have unique psychological characteristics[25]. However, it is not clear which personal characteristics (demographic variables) and which emotions, *e.g.*, depression, fear, neurasthenia, compulsive anxiety or hypochondria, exerted important effects in online learning satisfaction early in the epidemic. Furthermore, coping style is a cognitive and behavioral feature that individuals adopt when facing stressful situations and events. Coping style has a positive and a negative dimension[26]. Positive coping helps individuals to actively manage adversity, which involves asking for advice and finding solutions to adjust to stressors quickly and maintain mental well-being. Negative coping includes social withdrawal and avoidance. Negative coping can increase anxiety and depression and increase the degree of procrastination, which have a negative effect on academic performance [27]. Positive coping is a protective factor for mental health[28]. Nevertheless, factors associated with emergency online learning satisfaction such as coping style have not been adequately defined for the specific pandemic period. Thus, we measured the influence of different characteristics of college students, their psychological state and coping style on their learning satisfaction. Our findings will provide references for colleges to conduct accurate mental health education for students and ensure student satisfaction with online courses. Also, our findings provide understanding of the challenges to fostering a productive learning environment threatened by epidemic outbreak and economic uncertainty.

MATERIALS AND METHODS

Study design

This study was a cross-sectional investigation. An online questionnaire was generated by Wenjuanxing. Wenjuanxing is a web-based, widely used, open questionnaire platform which was developed by the Changsha Ranxing Information and Technology Limited Company. A General Information questionnaire, Psychological questionnaire for Emergent Events of Public Health, and a Simplified Coping Style Questionnaire (SCSQ) were used to measure online satisfaction with learning and associated factors, particularly personal characteristics, mental status, and coping style.

Participants and data collection

Study participants were undergraduates from four colleges and universities, Hebei Medical University, Hebei Normal University, Hebei Academy of Fine Arts, and Shijiazhuang Information Engineering Vocational College. Convenience sampling was used to select participants. Data collection was conducted between March 23, 2020 and April 9, 2020. Because of the pandemic, the students remained at home in different cities and received electronic questionnaires by WeChat. The questionnaire was distributed by school administrators or teachers.

Ethics statement

The study protocol was approved by the Ethics Committee of Hebei General University and complied strictly with ethical requirements. Ethics Review No. (2020) scientific ethics No. (30). All participants provided prior informed consent. Participants were informed that they were free to withdraw at any time. Participants were asked to respond on their own merits and complete survey items in accordance with standardized guidelines. Participant identities were anonymous.

General information questionnaire

The questionnaire was designed to investigate mainly demographic and sociological data, *i.e.*, gender, age, current role, grade, nationality, family location, academic year, monthly household income, parents' education, online status, average daily time paying attention to the epidemic, and whether bored at home for long time. In addition, online learning satisfaction, exercise intensity, and health status scores during the epidemic were rated 1-10 from "very dissatisfied or weak or poor" to "very satisfied, strong, good". Satisfaction scores were defined as poor (1-3), general (4-6), and good (7-10) for online courses.

Psychological Questionnaire for Emergent Events of Public Health

Mental status was assessed with Psychological Questionnaire for Emergent Events of Public Health[29]. This questionnaire is composed of 25 items of five subscales, depression, neurasthenia, fear, compulsion-anxiety, and hypochondria. Each item is scored according to a four-point Likert scale (0 = seldom to 3 = severe) or (0 = seldom to 3 = always). The higher the score of a dimension, the more serious the emotional reaction. The prompt "Possible attitude or practice toward COVID-19" was set to match the actual situation of this survey. The Cronbach's α of the questionnaire for this assessment was 0.776.

SCSQ

Coping styles were assessed with the SCSQ[30]. This questionnaire reflects the attitudes and practices adopted when one experiences setbacks or difficulties. The questionnaire included 20 items in 2 dimensions: Positive coping styles (12 items, *e.g.*, try to look on the bright side, find different ways to solve a problem) and negative coping styles (8 items, *e.g.*, relieve troubles by smoking and drinking, imagine a miracle will come). A 4-point scale was used for each item (0 = never, 1 = seldom, 2 = often, and 3 = always). The total score of the positive coping subscale was from 0 to 36, and the total score of the negative coping subscale was from 0 to 24. High scores reflected high levels of the indicated coping style. The internal consistency coefficients of the positive and negative coping subscale were 0.890 and 0.680, respectively.

Data analysis

Quantitative data were analyzed with descriptive and exploratory methods. First, the skewness and kurtosis values were used to determine whether the data were normally distributed. Data were skewed, continuous variables were expressed as median (interquartile range) and were assessed by Mann–Whitney test or Kruskal-Wallis H test. Second, the correlation of variables was represented by Pearson's and Spearman's coefficients based on the type of data. Third, multiple linear regression was performed to identify predictors of online learning satisfaction. All statistical analysis was performed using SPSS 22.0 (IBM Corporation). All tests were within the 95% confidence interval. When the confidence interval did not include zero, the mediating effect was significant at $P < 0.05$. A two-tailed P value of less than 0.05 was considered statistically significant.

RESULTS

Descriptive statistics

We collected 1600 questionnaires, of which 1580 (98.6%) were effective. The average answer time was 294 ± 165 S. The average age of the participants was 19.9 years (range 17-29 years). There were 342 men (21.6%) and 1238 women (78.4%). There were 191 (12.1%) medicine and 799 (50.6%) and 590 (37.3%) arts and science students. Online learning satisfaction was poor for 3.9% (61/1580) of participants, general for 33.2% (525/1580), and good for 62.9% (994/1580).

Demographic characteristics and single factor analysis

Table 1 lists demographic characteristics and single factor analysis. In the online learning satisfaction dimension, we found statistical significance ($P < 0.05$) for age, major, academic year, family location, online status, average time attention to epidemic, whether following a regular schedule, whether bored at home, health condition, and exercise intensity.

Correlation analysis of online learning satisfaction, mental status, and personal characteristics

We assessed the correlation matrix for all study variables (Table 2). Correlation analyses showed that fear, compulsion-anxiety, positive coping style, father's education, online status, exercise intensity, health condition, whether on a regular schedule, and whether bored at home were positively associated with online learning satisfaction. However, depression, neurasthenia, hypochondria, negative coping style, age, and average time of attention to the epidemic were negatively correlated with online learning satisfaction.

Multiple linear regression of online learning satisfaction

To avoid interaction and multicollinearity, we constructed three models. The dependent variable was learning satisfaction, after confounding factors were excluded. Online learning at schedule, strong exercise intensity, good health, regular schedule, paying attention to epidemic less than one hour, and not bored at home had positive effects ($P < 0.05$) on online learning satisfaction (Table 3). There was no statistical significance for other independent variables. Depression and neurasthenia had significant negative effects on online learning satisfaction, whereas fear positively affected online learning satisfaction ($P < 0.05$; Table 4). Positive coping had a significant positive effect on satisfaction with online courses, whereas negative coping had a significant negative effect ($P < 0.05$; Table 5).

DISCUSSION

The COVID-19 epidemic disrupted education systems, and college students had to turn to distance education quickly. Online learning satisfaction affected academic achievement. As such, it is critical to assess online learning satisfaction, and we need to be aware of some implications. In this study, we showed a relation between online learning satisfaction, personal characteristics, mental status, and coping style. We propose recommendations and solutions to enhance student online learning satisfaction.

We found that online learning satisfaction was reported good by 62.9% (994/1580) of study participants, but nearly half of college students were less satisfied with their studies. Similarly, Maqableh and Alia[31] found that more than a third of surveyed undergraduate students were dissatisfied with the online learning experience. Our results might suggest that emergency online learning could be an optional approach when surviving the shift during the COVID-19 pandemic. On the basis of similar studies, we suggest that a more plausible explanation is that online learning laid a good foundation for promoting interest, effective in learning because of its unlimited access, ease of use, flexibility, innovation,

Table 1 Demographic characteristics and single factor analysis among college students during coronavirus disease 2019 [median (interquartile range)], (*n* = 1580)

Variable	*n*	Online learning satisfaction	Depression	Neurasthenia	Fear	compulsion-anxiety	Hypochondria	Positive coping style	Negative coping style
Sex									
Female	1238	7.0 (2.0)	0.2 (0.5)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.5)	20.0 (11.0)	7.0 (5.0)
Male	342	7.0 (4.0)	0.3 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.2)	0.0 (0.0)	19.0 (13.0)	7.0 (6.0)
Z value		-0.56	-2.90	-0.09	-3.56	-1.86	-1.71	-1.56	-1.01
P value		0.606	0.004[2]	0.928	<0.001[2]	0.063	0.088	0.120	0.312
Age (yr)									
17-20	1219	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
21-29	361	7.0 (3.0)	0.3 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.5)	20.0 (11.0)	7.0 (2.00)
Z value		-3.27	-2.98	-2.46	-0.44	-0.53	-1.078	-0.77	-2.59
P value		< 0.001[2]	0.003[2]	0.014[1]	0.660	0.600	0.281	0.440	0.010[1]
Currently role									
Volunteers	44	7.0 (3.0)	0.3 (0.8)	0.2 (0.8)	0.5 (0.8)	0.0 (0.2)	0.0 (0.5)	17.5 (12.5)	7.5 (7.5)
At home	1536	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
Z value		-0.62	-1.66	-0.17	-0.03	-1.92	-1.57	-0.05	-0.84
P value		0.538	0.097	0.242	0.974	0.055	0.116	0.961	0.399
Major									
Medicine	191	7.0 (3.0)	0.3 (0.8)	0.4 (0.8)	0.5 (0.7)	0.0 (0.2)	0.0 (0.5)	19.0 (11.0)	7.0 (6.0)
Art	799	7.0 (2.0)	0.2 (0.5)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (6.0)
Science	590	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (10.0)	6.0 (5.0)
χ^2		14.80	14.42	12.20	2.54	-0.96	-0.32	7.76	7.01
P value		< 0.001[2]	< 0.001[2]	0.002[2]	0.281	0.617	0.850	0.021[1]	0.030[1]
Academic year									
1st	708	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	18.0 (12.0)	6.0 (7.0)
2nd	308	7.5 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.5)	20.0 (13.0)	7.0 (6.0)
3rd	430	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.6)	22.0 (10.3)	7.0 (5.0)
4th	134	7.0 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.8)	0.0 (0.2)	0.0 (0.5)	19.5 (11.3)	7.0 (6.0)

χ^2		13.48	-0.49	1.84	0.37	2.339	3.104	36.63	15.21
P value		0.004[2]	0.181	0.607	0.946	0.505	0.376	< 0.001[2]	0.002[2]
Family location									
Country	865	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.6)	0.0 (0.0)	19.0 (11.5)	7.0 (5.0)
Town	292	7.0 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.4)	20.0 (11.0)	7.0 (5.0)
City	423	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.2)	0.0 (0.0)	20.0 (12.0)	7.0 (6.0)
χ^2		10.24	4.73	1.75	0.38	4.42	0.101	16.05	10.77
P value		0.006[2]	0.093	0.417	0.829	0.110	0.951	< 0.001[2]	0.005[b]
Nationalities									
Ethnic minorities	71	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.8)	0.0 (0.0)	0.0 (0.0)	17.0 (11.0)	7.0 (5.0)
Han Chinese	1509	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (6.0)
Z value		-0.95	-0.74	-0.86	-0.49	-0.32	-1.03	-0.90	-0.47
P value		0.342	0.460	0.389	0.625	0.749	0.304	0.367	0.639
Whether student cadres									
Yes currently	770	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (11.0)	7.0 (5.0)
Used to be	436	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.2)	0.0 (0.0)	20.0 (11.0)	7.0 (6.0)
No	374	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (5.0)
χ^2		1.28	5.20	1.30	4.46	6.49	3.41	6.62	3.21
P value		0.528	0.074	0.521	0.108	0.039[a]	0.181	0.037[a]	0.201
Monthly household income (Yuan)									
< 5000	950	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
5000-10000	523	7.0 (2.0)	0.2 (0.5)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (6.0)
10000	107	7.0 (2.0)	0.3 (0.8)	0.4 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	20.0 (13.0)	8.0 (6.0)
χ^2		0.35	4.26	4.65	2.52	4.78	0.40	5.68	3.49
P value		0.840	0.119	0.098	0.284	0.092	0.819	0.058	0.174
Online status									
No network or not well	46	5.5 (3.0)	0.4 (1.2)	0.4 (1.3)	0.6 (0.7)	0.0 (0.5)	0.0 (0.1)	16.0 (12.3)	7.0 (7.5)
Can not online learning at schedule	16	4.0 (3.8)	0.8 (0.7)	1.0 (0.8)	0.8 (0.8)	0.1 (0.9)	0.0 (0.5)	17.0 (12.0)	8.0 (6.5)

Can online learning at schedule	1518	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (5.0)
χ^2		49.80	17.92	29.13	6.90	20.59	1.09	10.57	0.93
P value		< 0.001[2]	< 0.001[2]	< 0.001[2]	0.032[1]	< 0.001[2]	0.579	0.005[2]	0.628
Average time attention to epidemic									
Almost all day	165	7.0 (3.5)	0.0 (0.5)	0.2 (0.6)	0.7 (0.8)	0.0 (0.0)	0.0 (0.5)	20.0 (11.5)	7.0 (5.0)
About 1-3 h or more	231	8.0 (3.0)	0.2 (0.5)	0.2 (0.6)	0.7 (0.7)	0.0 (0.0)	0.0 (0.5)	21.0 (11.0)	6.0 (5.0)
< 1 h	1132	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (6.0)
Not concerned	52	5.0 (3.0)	0.2 (0.8)	0.2 (0.8)	0.3 (0.5)	0.0 (0.2)	0.0 (0.0)	14.5 (17.5)	6.5 (6.8)
χ^2		43.39	2.23	1.03	14.75	3.45	1.37	22.51	0.73
P value		< 0.001[2]	0.526	0.794	0.002[2]	0.327	0.713	< 0.001[2]	0.866
Whether regular schedule									
No	427	6.0 (3.0)	0.5 (0.7)	0.4 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	21.0 (12.0)	7.0 (5.0)
Yes	1153	7.0 (2.5)	0.0 (0.5)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	17.0 (9.0)	7.0 (5.0)
Z value		-9.97	-11.51	-9.979	-4.62	-7.05	-2.22	-6.32	-3.89
P value		< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	0.027[1]	< 0.001[2]	< 0.001[2]
Whether bored at home for long time									
Yes	643	7.0 (3.0)	0.3 (0.8)	0.4 (0.8)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	19.0 (9.0)	7.0 (5.0)
No	937	7.0 (2.0)	0.0 (0.5)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (5.0)
Z value		-6.86	-10.73	-9.54	-4.52	-6.86	-3.05	-2.31	-4.35
P value		< 0.001[2]	< 0.001[2]	<0.001[2]	< 0.001[2]	< 0.001[2]	0.002[2]	0.021[1]	< 0.001[2]
Mother's education									
Junior secondary and below	975	7.0 (2.0)	0.7 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
High School	358	7.0 (3.0)	0.7 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (6.0)
University and above	247	7.0 (2.0)	0.7 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	21.0 (13.0)	7.0 (6.0)
χ^2		3.38	0.23	0.33	1.85	0.67	0.50	2.08	2.27
P value		0.185	0.890	0.853	0.396	0.710	0.779	0.353	0.322
Father's education									
Junior secondary and below	963	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)

High School	348	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.8)	0.0 (0.0)	0.0 (0.5)	19.0 (12.0)	7.0 (6.0)
University and above	269	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.1)	0.0 (0.0)	20.0 (12.5)	7.0 (6.0)
χ^2		4.88	0.54	0.68	2.08	2.05	2.18	1.95	1.11
P value		0.087	0.763	0.711	0.354	3.359	0.337	0.378	0.575
Health condition									
Poor (grade 1-3)	28	4.5 (4.0)	0.9 (1.3)	0.9 (1.4)	0.7 (0.8)	0.2 (0.6)	0.0 (0.5)	14.0 (11.5)	8.5 (6.5)
General (grade 4-6)	239	6.0 (2.0)	0.5 (0.7)	0.6 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	17.0 (10.0)	8.0 (6.0)
Good (grade 7-10)	1313	7.0 (2.0)	0.2 (0.5)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	6.0 (5.0)
χ^2		168.63	113.22	91.40	20.51	97.75	21.05	24.56	21.62
P value		< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]
Exercise intensity									
Weak (grade 1-3)	272	5.0 (3.0)	0.5 (0.7)	0.4 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	17.5 (10.0)	8.0 (6.0)
General (grade 4-6)	702	7.0 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (11.3)	7.0 (6.0)
Strong (7-10)	606	8.0 (2.0)	0.0 (0.3)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	21.0 (12.0)	6.0 (6.0)
χ^2		382.38	129.73	91.37	21.38	43.24	17.25	17.13	22.50
P value		< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]	< 0.001[2]

[1]$P < 0.05$.
[2]$P < 0.01$ (two-tailed).

repeatedly watching for the future and review, and online learning was effective, applicable and acceptable in education [32]. However the challenge is to find the associated factors and take measures to improve satisfaction according to those factors.

Our findings indicated that college students who participated in online learning at schedule were more satisfied than students who could not get online either because of a lack of a schedule or no network accessibility. That is to say, online learning satisfaction may be related to the degree of participation. Similarly, Hensley *et al*[33] found that students who were able to participate in online courses at schedule had greater learning satisfaction and were more likely to complete their courses successfully. Also, mobile connections and the quality of internet were main factors related to student negative emotions that associated with the quality, performance, and timeliness of study obligations[34]. We suggest forming a home-school joint mechanism, constructing more and improving existing networks, and urging students to attend classes at schedule, to enhance participation and increase online learning satisfaction.

We found that strong exercise intensity, good health, and regular schedule were positively associated with learning satisfaction. Zhang *et al*[35] reported that college students who participated in physical activity < 3 d/wk had symptoms of depression compared with students who exercised ≥3 d/wk. There was also an interaction between long screen use,

Table 2 Correlation analysis of online learning satisfaction, mental status and characteristics

Factors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Online learning satisfaction	-															
Depression	-0.307[3]	-														
Neurasthenia	-0.245[3]	0.624[3]	-													
Fear	0.091[3]	0.381[3]	0.575[3]	-												
Compulsion-anxiety	0.193[3]	0.531[3]	0.490[3]	0.301[3]	-											
Hypochondria	-0.075[2]	0.271[3]	0.397[3]	0.463[3]	0.289[3]	-										
Positive coping style	0.122[3]	-0.085[2]	-0.089[3]	0.057[1]	-0.104[3]	-0.001	-									
Negative coping style	-0.089[3]	0.274[3]	0.264[3]	0.220[3]	0.212[3]	0.162[3]	0.363[3]	-								
Age	-0.093[3]	0.069[2]	0.054	0.030	0.005	0.043	0.023	0.036	-							
Father's education	0.055[1]	0.005	-0.018	-0.024	0.024	-0.013	0.031	0.026	-0.057[1]	-						
Online status	0.171[3]	-0.099[3]	0.118[3]	-0.044	0.111[3]	-0.017	0.080[2]	-0.020	-0.018	-0.019	-					
Exercise intensity	0.537[3]	-0.305[3]	-0.264[3]	-0.119[3]	-0.169[3]	-0.097[3]	0.111[3]	-0.113[3]	-0.184[3]	0.044	0.073[2]	-				
Health condition	0.418[3]	-0.351[3]	-0.298[3]	-0.166[3]	-0.290[3]	-0.182[3]	0.101[3]	-0.161[3]	-0.180[3]	0.020	0.096[3]	0.462[3]	-			
Average time attention to epidemic	-0.132[3]	0.035	-0.005	-0.088[3]	0.023	-0.029	-0.094[3]	0.010	0.019	-0.016	-0.022	-0.144[3]	-0.138[3]	-		
Whether regular schedule	0.251[3]	-0.290[3]	-0.251[3]	-0.116[3]	-0.177[3]	-0.056[1]	0.159[3]	-0.098[3]	-0.044	0.060[1]	0.105[3]	0.284[3]	0.224[3]	-0.030	-	
Whether bored at home for long time	0.173[3]	-0.270[3]	-0.204[3]	-0.114[3]	-0.173[3]	-0.077[2]	0.058[1]	-0.110[3]	-0.053[1]	-0.013	0.091[3]	0.121[3]	0.104[3]	-0.016	0.183[3]	-

[1]$P < 0.05$.
[2]$P < 0.01$.
[3]$P < 0.001$ (two-tailed).

less physical activity, and symptoms of depression. High levels of depression were associated with difficulty in paying attention to academics[36] and ultimately deficient learning satisfaction. A poor physical condition leads to lack of energy, which directly affects learning satisfaction. College students who work and sleep irregularly often use the screen too long before going to bed; this behavior can cause sleep deprivation and sleep rhythm disorder, increased sleep-related disorders[37], induced adverse emotions such as anxiety and depression[38], affected cognitive function and learning [39], and eventually poor learning satisfaction. Also, sleep disturbance predicts the development and persistence of posttraumatic stress disorder and depression[40] which impair health and academic performance. Therefore, we suggest that a network interactive platform of individual-family-school-society should be established as an effective linkage mechanism to make sports and exercise programs congenial and encourage college students to participate in sports and exercise at home, or receive exercise prescription teaching to mobilize student initiative, enthusiasm, an consciousness,

Table 3 Demographic characteristics with online learning satisfaction (Model 1)

Variable	Unstandardized coefficients		Standardized coefficients beta	*t* value	*P* value
	B	Std. Error			
Can online learning at schedule (reference)					
Can not online learning at schedule	-2.490	0.394	-0.129	-6.327	< 0.001
No network or not well	-0.981	0.236	-0.085	-4.156	< 0.001
Exercise intensity	0.334	0.020	0.401	16.860	< 0.001
Health condition	0.166	0.025	0.158	6.671	< 0.001
Whether regular schedule					
No (reference)					
Yes	0.266	0.094	0.061	2.828	0.005
Average time attention to epidemic					
< 1 h (reference)					
Not concerned	-0.889	0.223	-0.082	-3.989	< 0.001
Whether bored at home for long time					
Yes (reference)					
No	0.343	0.082	0.087	4.199	< 0.001

Table 4 Metal status with online learning satisfaction (Model 2)

Variable	Unstandardized coefficients		Standardized coefficients beta	*t* value	*P* value
	B	Std. Error			
Depression	-0.776	0.134	-0.199	-5.807	< 0.001
Neurasthenia	-0.654	0.151	-0.163	-4.334	< 0.001
Fear	0.337	0.111	0.087	3.031	0.002

Table 5 Metal status with online learning satisfaction (Model 3)

Variable	Unstandardized coefficients		Unstandardized coefficients	*t* value	*P* value
	B	Std. Error			
Positive coping style	0.040	0.006	0.172	6.383	< 0.001
negative coping style	-0.061	0.012	-0.140	-5.183	< 0.001

and to expand personalities[41]. As well, students need to keep regular bedtimes and wake-up times to promote physical and mental health and ensure online learning satisfaction.

Our data suggest that low levels of online learning satisfaction were more likely to be reported by students who spent more than one hour per day looking for information about COVID-19. Previous studies have been focused on the relation between depression, anxiety, and online learning satisfaction. Wong *et al*[42] reported that students who had poor online learning satisfaction were more likely to experience stress. Kecojevic *et al*[36] found that students who spent more than an hour a day searching for information about COVID-19 were more likely to report higher levels of anxiety, depression, and somatization. These findings demonstrate that excessive attention to the epidemic was associated with high levels of anxiety, depression, and difficulty paying attention to academics, which led to low academic satisfaction. Additionally, there should be organized learning about COVID-19 to improve protection skills and avoid gossip and information overload.

Our findings indicate that college students who were bored staying at home for a long time were more likely to experience poor online learning satisfaction. Giusti *et al*[43] reported that students who studied at home either alone or with classmates were nearly three times more likely to have poor academic performance. Li *et al*[44] found that college students who lived at home for a long time tended to lack social interaction and support, and they felt lonely; family dysfunction, low social support, and low physical exercise have negative impacts on mental status. Similarly, Wissing *et*

al[45] mentioned that perceived peer support can promote collaborative learning and improve medical student learning satisfaction and participation. Therefore, in a special period of limit, we suggest that relevant organizations guide college students to increase contact and interaction with teachers and classmates and provide social and family support to promote positive feelings of long-term home confinement.

We found that high levels of depression and neurasthenia and negative coping styles had negative effects on online learning satisfaction, whereas positive coping styles had positive effects. On the basis of the control-value theory, investigators consider academic emotion to be an important factor that affects student learning satisfaction and academic performance in online learning context; negative adaptive coping strategies are associated with depression and anxiety [46]. Loneliness causes depression and anxiety, whereas procrastination completely mediates the effect of depression on academic performance[47]. Neurasthenia did not disappear; it continues to enjoy a marginal life in international classification schemes and is a common diagnosis in China[48]. Also, International Classification of Diseases (ICD)-11 Bodily Distress Disorder encompasses Neurasthenia which in the ICD-10 was classified in the grouping of "Other neurotic disorders"[49]. Huang *et al*[50] reported that 23.5% of adolescents were prone to anxiety, of which 1.7% had severe anxiety, and 26.3% of adolescents were prone to depression, of which 1.4% had severe depression. Therefore, on the basis of a study by Liu *et al*[51], we suggest that college students who experienced depressive disorders not only need support and personalized interventions from educators and school administrators, but also they need professional interventions such as cognitive behavioral therapy and online medication therapy from psychologists and psychiatrist. College student personality and psychology are still in a period of maturation. The coping styles of college students are closely related to their psychological health and learning satisfaction. Positive, mature coping is a protective factor of mental health, and it promotes developing individual adaptation. Negative, immature coping has a negative effect on mental health. To alleviate symptoms of depression, young adults who experience stressful life events may need to reinforce problem-focused coping and minimize emotion-focused coping strategies[52]. Therefore, we suggest that educators train student positive coping styles when conducting psychological intervention and educate and help students to adopt positive coping styles such as self-adjustment, help-seeking, and problem-solving. Doing so will improve college student mental health and online study satisfaction.

Our study may have some limitations. Considering differences in individual physical quality and endurance, we choose the ten grades of exercise intensity and did not use the sports scale. A standardized exercise intensity scale can be used to further refine our study. Interestingly, we found that fear was positively related to online learning satisfaction. As is well known, moderate anxiety or fear of failure in learning can motivate, and high fear of COVID-19 may have kept college students alert, promoted study of relevant topics, and mobilized their subjective initiative to respond positively, which may have increased online learning satisfaction. However, Al-Nasa'h *et al*[53] reported that fear of COVID-19 diminished the satisfaction of online learning. This difference may be related to differences in scales, sample sizes, and regions used in each study. We enrolled a large number of participants located in one metropolis of China. Hence, samples from other contexts are needed to assess the generality of our findings.

CONCLUSION

Our findings enrich our understanding about the impact of the COVID-19 pandemic on satisfaction of the college population toward emergency online learning. Although there was high online learning satisfaction, online education is still an imperfect substitute for in-person learning. College student online learning satisfaction was affected by whether it was scheduled and by depression, neurasthenia, fear, exercise intensity, attention to the epidemic, emotion at home, and coping style during the early stage of COVID-19. We suggest that college students with different characteristics should receive attention at different levels. Psychological intervention should be conducted, publicity and knowledge about COVID-19 should be strengthened, interaction between teachers and students and classmates should be strengthened when teaching online, and support from family and school should be enhanced to alleviate bad emotions that affect online learning satisfaction. Additionally, online group or individual psychological assistance, even psychotropic drugs for high-risk groups, should be made available. Students should adjust coping style and strengthen psychological defense skills. Students, families, schools, and the community can establish a joint mechanism. Related institutions can form mental health guidelines to promote safe and effective learning and a healthy life.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic disrupted all facets of everyday life. Students turned to online education to minimize the pandemic's spread and negative impacts on health. Students from various backgrounds and places were required to adapt to new learning conditions. Student learning satisfaction is a crucial indicator of the effectiveness of online learning that is related to academic achievement.

Surveys of online learning satisfaction during the COVID-19 pandemic show inconsistent results. Some studies showed that the higher the psychopathology scores, the less online learning satisfaction. University period is a critical time for shaping a student's personality and developing talents, they have unique psychological characteristics. However, it is not clear which personal characteristics (demographic variables) and which emotions, e.g., depression, fear, neurasthenia, compulsive anxiety or hypochondria, had important effects in online learning satisfaction early in the pandemic.

Furthermore, coping style is a cognitive and behavioral feature that individuals adopt when they face stressful situations and events. Coping style has a positive and a negative dimension. Positive coping helps individuals to actively manage adversity. Negative coping includes social withdrawal and avoidance. Negative coping can increase anxiety and depression and increase the degree of procrastination, which have negative effects on academic performance. Positive coping is a protective factor for mental health. Nevertheless, factors associated with emergency online learning satisfaction such as coping style have not been adequately defined for the specific pandemic period.

Research motivation

Our study will clarify satisfaction with online learning and identify personal characteristics and the emotions that had important effects on online learning satisfaction early in the pandemic. Furthermore, this study will clarify which coping style was associated with emergency online learning satisfaction in the specific period. Our findings will provide references for colleges to conduct accurate mental health education and ensure student satisfaction with online courses for a good quality academic experience and metal health.

Research objectives

Our objective is to provide references for colleges to conduct accurate mental health education for students and ensure their satisfaction with online courses. In addition, we will explain challenges to fostering a productive learning environment threatened by epidemic outbreak and economic uncertainty.

Research methods

We measured the influence of college student psychological states and coping styles on their learning satisfaction. Measurements were based on questionnaires designed to investigate mainly demographic and sociological data, *i.e.*, gender, age, current role, grade, nationality, family location, academic year, monthly household income, parents' education, online status, average daily time paying attention to the epidemic, and whether bored at home for long time. Mental status was assessed with the Psychological Questionnaire for Emergent Events of Public Health (PQEEPH). The PQEEPH scale is specially designed for public health emergencies; it is composed of 25 items of five subscales, *i.e.*, depression, neurasthenia, fear, compulsion-anxiety, and hypochondria that describe emotional status precisely and in detail. Coping styles were assessed with the Simplified Coping Style Questionnaire. Quantitative data were analyzed with descriptive and exploratory methods. First, the skewness and kurtosis values were used to determine whether the data were normally distributed. Data were skewed, continuous variables were expressed as median (interquartile range) and were assessed by Mann–Whitney test or Kruskal-Wallis H test . Second, the correlation of variables was represented by Pearson's and Spearman's coefficients based on the type of data. Third, multiple linear regression was performed to identify predictors of online learning satisfaction. All statistical analysis was performed using SPSS 22.0 (IBM Corporation). All tests were within the 95% confidence interval.

Research results

We collected 1600 questionnaires, of which 1580 (98.6%) were effective. Online learning satisfaction was poor for 3.9% (61/1580) of participants, general for 33.2% (525/1580) participants, and good 62.9% (994/1580). Demographic characteristics and single factor analysis showed statistical significance ($P < 0.05$) for age, major, academic year, family location, online status, average time attention to epidemic, whether following a regular schedule, whether bored at home, health condition, and exercise intensity. Correlation analysis of online learning satisfaction, mental status, and personal characteristics showed that fear, compulsion-anxiety, positive coping style, father's education, online status, exercise intensity, health condition, whether on a regular schedule and whether bored at home were positively associated with online learning satisfaction. Depression, neurasthenia, hypochondria, negative coping style, age, average time of attention to the epidemic were negatively correlated with online learning satisfaction. Multiple linear regression of online learning satisfaction showed online learning at schedule, strong exercise intensity, good health, regular schedule, paying attention to epidemic less than one hour, and not bored at home had positive effects ($P < 0.05$) on online learning satisfaction. Depression and neurasthenia had significant negative effects on online learning satisfaction, whereas fear had positive effects ($P < 0.05$). Positive coping had a significant positive effect on satisfaction with online courses, whereas negative coping had a significant negative effect ($P < 0.05$).

Research conclusions

The new theory is that this study assessed factors especially on personal characteristics, mental status, and coping style related to satisfaction with emergency online learning among college students during the COVID-19 pandemic. Little study has been focused on online acceptance of education in early time of COVID-19 pandemic. Our findings provide reference for educators, psychologists, and school administrators to conduct health education intervention.

The new method we used is the PQEEPH. This scale is specially designed for public health emergencies, it is composed of 25 items of five sub scales, depression, neurasthenia, fear, compulsion-anxiety, and hypochondria which describe the emotional status detailed and precisely.

Research perspectives

On the basis of our methods and findings concerning factors that affect online learning satisfaction, we suggest that it will be possible to assess the effects of psychological intervention for college students during the next emergency online learning period and then formulate corresponding and mature programs.

FOOTNOTES

Author contributions: Wang XY and Ni AH contributed to conception and design of the study; Jing P organized the database; Zhao Y, Zhang K, Lei DC, and Han JT collected data; Zhai XY performed the statistical analysis and write the article; All authors contributed to manuscript revision, read, and approved the submitted version.

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ORIGINAL ARTICLE

Observational Study

Influence of physical education on anxiety, depression, and self-esteem among college students

Hai-Yan Fu, Jing Wang, Jia-Xi Hu

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Abstract

BACKGROUND

Physical education is pivotal in our country's education reform. Urban schools have notably enhanced the intensity of physical education in recent years. However, the effects of physical education on students' anxiety, depression, and self-esteem levels, as well as their interrelations, remain unexplored.

AIM

To analyze the influence of physical education on students' anxiety, depression, and self-esteem.

METHODS

This study employed a cross-sectional design. A stratified cluster sampling method was used to select 478 first-year university students. Self-administered questionnaires were used to investigate the physical education status and basic information of college students. We used the Physical Activity Rank Scale-3 (PARS-3), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Self-Esteem Scale (SES) to assess the level of exercise, anxiety, depression, and self-esteem. Multiple Logistic regression was used to analyze the factors influencing anxiety, depression, and low self-esteem. The receiver operating characteristic curve and area under the curve (AUC) were used to evaluate the predictive ability of PARS-3 scores for anxiety, depression, and low self-esteem. Spearman's correlation was used to analyze the correlations among the PARS-3, SAS, SDS, and SES.

RESULTS

Compared with the domestic norms, SAS and SDS scores were higher, and SES scores were lower ($P < 0.05$). Among the participants, 210 (43.93%) had PARS-3 scores below 20, 94 (19.67%) had scores of 20-42, and 174 (36.40%) had scores above 42. After adjusting for daily sleep time, gender, being an only child, major, father's educational background, mother's educational background, and family

residence, PARS-3 scores were independent influencing factors for anxiety, depression, and low self-esteem (P < 0.05). The AUC of PARS-3 scores predicting anxiety, depression, and low self-esteem were 0.805 (0.760-0.849), 0.799 (0.755-0.843), and 0.831 (0.788-0.874), respectively. The sensitivities were 0.799, 0.801, and 0.748, and the specificities were 0.743, 0.716, and 0.814, respectively. PARS-3 was negatively correlated with SAS and SDS scores (r = -0.566, -0.621, both P < 0.001) and positively correlated with SES scores (r = -0.621, P < 0.001). SES scores were negatively correlated with SAS and SDS scores (r = -0.508, r = -0.518, both P < 0.001).

CONCLUSION

The amount of physical activity is negatively correlated with anxiety and depression degree and positively correlated with self-esteem degree.

Key Words: Physical education; Student; Anxiety; Depression; Self-esteem; Influence

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Core Tip: This study establishes a negative correlation between physical activity levels and the degree of anxiety and depression while demonstrating a positive correlation with self-esteem. This provides substantial evidence for the impact of physical education on anxiety, depression, and self-esteem of college students.

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INTRODUCTION

University physical education aims to promote students' holistic development and cultivate students' comprehensive quality through sports activities[1]. Physical activity is a reliable way to develop healthy behaviors, sports abilities, morality, and other qualities among students[2]. College students are under pressure from various aspects, such as college entrance, interpersonal conflict, and job search competition. Moreover, they are prone to psychological problems, such as anxiety and depression, which may lead to violent injuries and even suicide[3]. Self-esteem refers to confidence in one's worth, abilities, and morals[4]. Self-esteem is a positive psychological quality and psychological capital for college students' growth and success[5]. College students are an important part of young people, and their physical and mental health have an important influence on personal development and long-term national planning. Research has shown that individuals with low self-esteem are prone to anxiety, depression, and other negative emotions[6]. However, individuals with high self-esteem have varying mental health levels[7]. Appropriate physical activity reduces anxiety and depression among college students[8] and effectively improves their self-esteem[9]. However, studies on the effects of physical education on anxiety, depression, and self-esteem are scant. Therefore, we used college students to analyze the influence of physical education on anxiety, depression, and self-esteem to provide a reference for improving their physical and mental health.

MATERIALS AND METHODS

Object of study

We conducted a cross-sectional survey. We selected university students using stratified cluster sampling. The participants were based on major, including humanities and social sciences, science and engineering, and medical sciences. Three majors were selected to obtain a sufficient sample size.

We determined the sample size using a formula (quantitative variable)[10] for cross-sectional studies: $n = (\frac{Z_{1-\alpha/2}\times\sigma}{\delta})^2$, where: n represents the sample size of each group; $Z_{1\text{-alpha}/2}$ = 1.96; δ represents the allowable error, which is the half-width of the confidence interval; and sigma is the standard deviation. Based on δ = 5 and σ = 30, we calculated n to be 139. Considering a 10% withdrawal rate, we estimated that the study required 459 participants [139 × 3 × (1 + 10%)].

The survey object recruitment methods were as follows: Buy some small gifts, such as carbon pens, cartoon erasers, post-it notes, and other small prizes, for each person willing to participate in the survey. The students included in the survey have the spirit, consciousness, ability, and a WeChat account to complete the questionnaire independently. They knowingly and voluntarily agree to participate in this study. We excluded the students who could not complete the questionnaire for any reason. To protect privacy, we ensure the questionnaire results and data are only known by the research team and destroy the questionnaire after obtaining the relevant data analysis conclusions. We established a WeChat group of survey participants and, after obtaining informed consent, sent questionnaire links to the group for the

questionnaire survey. Participation was voluntary. We sent 500 questionnaires, and 486 were returned (97.2% recovery rate). After excluding the invalid questionnaires such as missing or multiple pages, incomplete filling, respondents not meeting the requirements, obviously wrong or incorrect answers, or recalled deadlines, we included 478 effective questionnaires (95.6%) in the analysis.

Questionnaire survey and quality control

We used original questionnaires that were reviewed and tested by experts. The audit includes the completeness, standardization, consistency, authenticity, effectiveness, feasibility, and scientificity of the questionnaire. A test is a form of survey used to obtain preliminary information and understand respondents' opinion before conducting a formal survey. The questionnaire obtained information on the participants, their parents, and their peers. The survey included questions regarding sociodemographic factors, physical activity, anxiety, depression, and self-esteem. The survey was conducted from February to May 2023.

The investigators in this study were members of a research group that had undergone unified training and assessment. They managed the research data and survey results. Participants who were unable to participate in the survey during the set period were contacted by the investigators within two weeks and requested to complete the questionnaire using the same procedure as the set survey to reduce the number of invalid questionnaires.

Sociodemographic factors

Based on a review of the relevant literature, we designed a sociodemographic questionnaire under the guidance of epidemiologists. The questions included student number, gender, being an only child, major, parents' educational background, family residence, and average daily sleep time over the last month.

Sports activities

We employed the Physical Activity Rank Scale-3 (PARS-3)[11] to calculate the participants' physical activity in the past month. In previous studies, the scale's internal consistency and reliability were 0.86 and 0.82, respectively. The scale contains three dimensions: time, intensity, and frequency of exercise. Items were rated on a five-point Likert scale (1 = light exercise; 5 = competitive exercise). Among them, exercise time was rated 0 to 4 points, and exercise intensity and frequency grades were 1 to 5 points. Exercise was calculated as time × intensity × frequency; the score range was 0 to 100 points. Exercise classification criteria were as follows: ≤ 19 points = low exercise, 20-42 points = moderate exercise, ≥ 43 points = high exercise.

Anxiety and depression

We used the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS)[12] to detect anxiety and depression, respectively. The SAS contains 20 items (15 positive and 5 reverse scores). Similarly, the SDS contains 20 items (11 positive and nine reverse scores). Items were rated on a four-point Likert scale (1 = occasional; 4 = persistent). The sum of the scores for each item was the approximate score of anxiety or depression. The standard or final score of anxiety or depression was calculated as 1.25 times the score of anxiety or depression rounded to a whole number. The criteria for identifying anxiety were an SAS score of > 50 points while depression was an SDS score of > 53 points.

Self-esteem

We employed the Self-Esteem Scale (SES)[13] to evaluate college students' self-esteem. The scale's internal consistency was 0.87 in previous studies. This scale contains ten items (five positive and five negative). Items were rated on a four-point Likert scale (1 = strongly disagree; 4 = strongly agree). The total self-esteem score was the sum of all entries. Higher SES scores indicated higher self-esteem.

Statistical analysis

We used SPSS 20.0 to process the data and expressed the measurement data as mean ± SD. Comparisons between two sets of data were performed using the *t*-test, and comparisons between three sets of data were performed using a one-way analysis of variance (ANOVA) and Bonferroni. Count data are represented as *n*.

We classified low self-esteem by subtracting one standard deviation from the domestic norm average of SES[14]. Anxiety (anxious = 1, not anxious = 0), depression (depressed = 1, not depressed = 0), and self-esteem (low self-esteem = 1, regular/high self-esteem = 0) were the dependent variables, whereas PARS-3 scores and sociodemographic indicators were the independent variables. A multivariate logistic regression model was used for the analysis. The predictive ability of the receiver operator characteristic curve (ROC) and area under the curve (AUC). Spearman's correlation analysis was used to explore the correlation between PARS-3 scores and SAS, SDS, and SES scores. A *P* value less than 0.05 means that the difference is statistically significant.

RESULTS

SAS, SDS, and SES scores

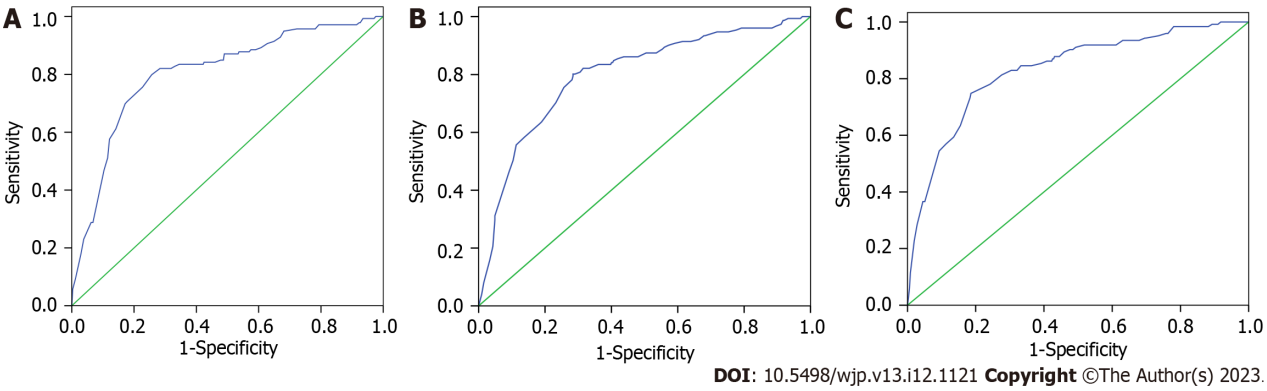
The participants' SAS and SDS scores were higher and SES scores were lower than the domestic norms [SAS: (29.78 ± 10.07) points, SDS: (33.46 ± 8.55) points][15,16] ($P < 0.05$; Table 1).

Table 1 Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Self-Esteem Scale scores (*n* = 478)

Items	SAS	SDS	SES
Participants	46.39 ± 7.26	48.22 ± 10.24	26.35 ± 4.31
Domestic norm	29.78 ± 10.07	33.46 ± 8.55	28.75 ± 4.86
t^1	53.067	37.365	-12.184
P value	< 0.001	< 0.001	< 0.001

[1]Single sample *t*-test.

SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SES: the Self-Esteem Scale.



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Figure 1 Receiver operating characteristic curve of Physical Activity Rank Scale-3 scores predicting anxiety, depression, and low self-esteem. A: Physical Activity Rank Scale-3 (PARS-3) scores predicting anxiety; B: PARS-3 scores predicting depression; C: PARS-3 scores predicting low self-esteem.

Influence of sociodemographic factors on PARS-3 scores

Among the participants, 210 (43.93%) had PARS-3 scores ≤ 19, 94 (19.67%) scored 20-42, and 174 (36.40%) scored ≥ 43. Among the participants with PARS-3 scores ≤ 19, the PARS-3 scores of only children were higher than those who were not only children. The PARS-3 scores of college students with an average daily sleep time > 8 h were higher than those with an average daily sleep time of 6-8 h and those with an average daily sleep time of < 6 h (all $P < 0.05$; Table 2).

Influence of sociodemographic factors on SAS, SDS, and SES scores

The SDS scores of college students whose fathers' education was at or above the graduate level were higher than those of those whose fathers' education was less than the graduate level, and their SES scores were lower than those of those whose fathers' education was below the graduate level ($P < 0.05$; Table 3).

Factors influencing anxiety, depression, and low self-esteem

Anxiety (anxious = 1, not anxious = 0), depression (depressed = 1, not depressed = 0), and self-esteem (low self-esteem = 1, regular/high self-esteem = 0) were the dependent variables, whereas PARS-3 scores and sociodemographic indicators were the independent variables. A multivariate logistic regression model was used for the analysis (Table 4). The results showed that after adjusting for daily sleep time, gender, being an only child, major, father's educational background, mother's educational background, and family residence, PARS-3 scores were independent influencing factors for anxiety, depression, and low self-esteem ($P < 0.05$; Table 5).

Predictive ability of PARS-3 scores

The AUC of the PARS-3 scores predicting anxiety, depression, and low self-esteem were 0.805 (0.760-0.849), 0.799 (0.755-0.843), and 0.831 (0.788-0.874), respectively. The sensitivities were 0.799, 0.801, and 0.748 and the specificities were 0.743, 0.716, and 0.814, respectively (Figure 1, Table 6).

Correlation analysis between PARS-3 scores and SAS, SDS, and SES scores

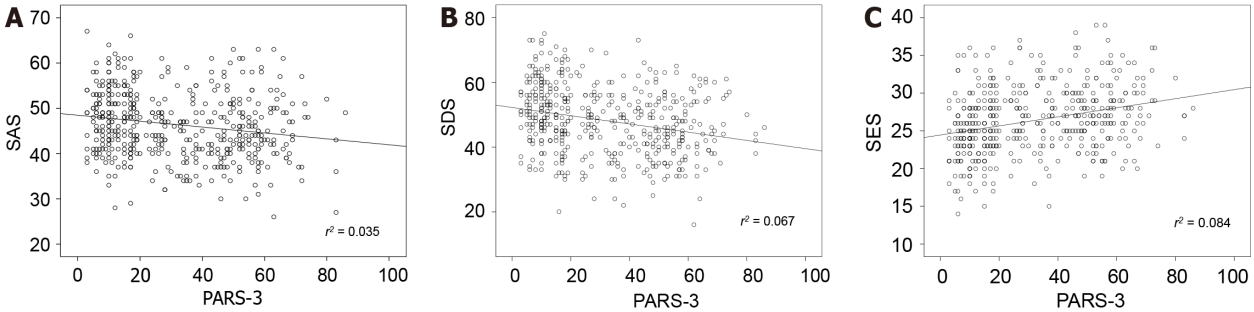
PARS-3 scores were negatively correlated with SAS and SDS scores (r = -0.566, -0.621, both $P < 0.001$) and positively correlated with SES scores ($r = -0.621$, $P < 0.001$). SES was negatively correlated with SAS and SDS scores ($r = -0.508$, $r = -0.518$, both $P < 0.001$; Figure 2, Table 7).

Table 2 The influence of sociodemographic factors on Physical Activity Rank Scale-3 scores

Index		Participant number	Statistic	PARS-3 scores		
				≤ 19	20-42	≥ 43
Gender	Male	221		11.60 ± 4.83	30.46 ± 5.77	56.50 ± 8.24
	Female	257		11.82 ± 4.41	32.27 ± 5.74	55.61 ± 9.62
			t	0.3446	1.544	0.637
			P value	0.731	0.126	0.525
Only child	Yes	212		12.42 ± 4.53	31.92 ± 6.01	56.59 ± 9.49
	No	266		11.14 ± 4.59	30.88 ± 5.65	55.49 ± 8.65
			t	2.023	0.866	0.792
			P value	0.044	0.388	0.429
Major	Humanities and social sciences	155		11.45 ± 4.64	30.34 ± 5.07	55.37 ± 8.62
	Science and engineering	135		12.04 ± 4.56	32.70 ± 5.92	57.49 ± 8.76
	Medicine	188		11.71 ± 4.60	31.20 ± 6.08	55.20 ± 9.61
			F	0.252	1.089	1.122
			P value	0.778	0.341	0.328
Father's educational background	High school or technical secondary school and below	210		11.58 ± 4.72	31.10 ± 5.63	55.63 ± 9.53
	College or undergraduate	205		11.96 ± 4.54	32.29 ± 5.28	55.33 ± 8.18
	Postgraduate and above	63		11.27 ± 4.06	30.14 ± 6.65	58.96 ± 9.89
			F	0.243	0.974	1.696
			P value	0.785	0.382	0.187
Mother's educational background	High school or technical secondary school and below	221		11.68 ± 4.76	31.07 ± 5.54	55.36 ± 9.92
	College or undergraduate	203		11.71 ± 4.53	31.67 ± 5.94	55.76 ± 7.75
	Postgraduate and above	54		12.08 ± 3.66	31.21 ± 6.21	58.70 ± 10.01
			F	0.041	0.104	1.240
			P value	0.960	0.901	0.292
Family domicile	Village	208		11.92 ± 5.18	30.07 ± 5.47	55.48 ± 9.30
	County	117		11.22 ± 4.27	33.60 ± 4.36	56.40 ± 9.26
	Downtown	153		11.86 ± 3.93	31.46 ± 6.51	56.39 ± 8.52
			F	0.442	2.642	0.215
			P value	0.644	0.077	0.807
Average sleep time	< 6 h	83		10.24 ± 4.71	29.87 ± 5.98	54.14 ± 9.41
	6-8 h	257		12.36 ± 4.43	31.29 ± 5.86	55.83 ± 8.60

> 8 h	138[a]		11.72 ± 4.57	32.15 ± 5.48	57.04 ± 9.55
		F	3.512	0.740	0.845
		P	0.032	0.480	0.431

[a]*P* < 0.05, compared to the average daily sleep time of 6-8 h and < 6 h.
PARS-3: Physical Activity Rank Scale-3.



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Figure 2 Scatter plot of correlation between Physical Activity Rank Scale-3 scores and Self-Rating Anxiety Scale, Self-Rating Depression Scale, and the Self-Esteem Scale scores. A: The correlation between Self-Rating Anxiety Scale and Physical Activity Rank Scale-3 (PARS-3); B: The correlation between Self-Rating Depression Scale and PARS-3; C: The correlation between the Self-Esteem Scale and PARS-3. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SES: the Self-Esteem Scale; PARS-3: Physical Activity Rank Scale-3.

DISCUSSION

Self-esteem affects how individuals deal with stressful events; individuals with high self-esteem are more inclined to adopt positive coping strategies to deal with stress[17]. Understanding the link between physical education and anxiety, depression, and self-esteem helps guide and intervene to promote students' holistic physical and mental development.

The amount of exercise, also known as exercise load, refers to the physical load, psychological load, and calories consumed by the human body during physical activity. Exercise load determines the intensity, duration, accuracy, and characteristics of the exercises. This study revealed anxiety, depression, and low self-esteem among college students, which require attention. The proportion of students with low physical activity was lower than that reported by Sheng *et al* [18]. However, the overall situation is not positive, and the potential impact of low physical activity on the physical and mental health of college students should be monitored. This may be due to the wide use of electronic products, such as smartphones and tablet computers. Several college students are addicted to mobile phones and the internet, reducing their willingness to participate in sports activities[19]. Some researchers have proposed that the lack of exercise among college students is related to a lack of good exercise habits due to academic pressure in middle school[20]. Students in middle school did not develop good exercise habits, and their bad exercise habits after college cannot be corrected in time, resulting in less exercise. Moreover, our findings suggest that college students with high physical activity levels have a lower risk of anxiety, depression, and low self-esteem. Furthermore, our results indicate that higher amounts of exercise are associated with reduced anxiety and depression and improved self-esteem among college students. Participation in sports activities can affect anxiety and depression levels in many ways. Sports activities can increase communication between college students and their peers and release negative emotions, thereby reducing anxiety and depression. Additionally, regular participation in sports activities can improve college students' sense of self-efficacy, thus enhancing their subjective support levels, problem-solving ability, and positive evaluation of volitivity and self-confidence[21]. Therefore, college students who are more active and proactive in coping with pressure have fewer negative emotional experiences and more positive emotional experiences, thus reducing anxiety and depression levels [22]. Moreover, physical exercise increases the relative content of metabolites 4-hydroxyphenyl lactate and dihydro thymine and decreases the relative content of glutamine in the human body, thus affecting the regulatory pathways related to negative emotions, such as coenzyme Q biosynthesis, tyrosine metabolism, and pyrimidine metabolism[23]. In addition, physical exercise can change the composition of the human intestinal flora, affecting the secretion of a series of substances that regulate neural activity, such as serotonin, and improving the level of anxiety and depression in individuals[24]. Therefore, we suggest that schools encourage college students to participate actively in physical exercise. Psychological education departments should pay attention to the mental health status of college students with low daily physical activity and implement effective intervention measures to prevent anxiety and depression.

This study found that higher amounts of exercise are associated with higher self-esteem among college students, which was in line with Zayed's findings[25]. Previous research has shown that physical exercise can improve self-esteem by reducing loneliness. Moreover, physical activity enhances self-esteem[26]. Activity time, frequency, and intensity may be the key factors that produce positive psychological benefits for self-esteem. Our findings indicated that lower self-esteem

Table 3 Influence of sociodemographic factors on Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Self-Esteem Scale scores

Index		Participant number	Statistic	SAS	SDS	SES
Gender	Male	221		46.63 ± 7.19	48.46 ± 9.50	26.36 ± 4.37
	Female	257		46.18 ± 7.31	48.01 ± 10.84	26.33 ± 4.26
			t	0.676	0.479	0.076
			P value	0.499	0.632	0.940
Only child	Yes	212		46.24 ± 6.74	48.58 ± 9.95	26.21 ± 4.21
	No	266		46.51 ± 7.65	47.93 ± 10.47	26.45 ± 4.39
			t	0.404	0.689	0.605
			P value	0.686	0.491	0.546
Major	Humanities and social sciences	155		45.95 ± 7.08	48.48 ± 9.47	26.62 ± 4.46
	Science and engineering	135		46.36 ± 6.97	48.33 ± 10.61	26.12 ± 4.13
	Medicine	188		46.76 ± 7.58	47.91 ± 10.58	26.28 ± 4.30
			F	0.531	0.144	0.522
			P value	0.588	0.866	0.594
Father's educational background	High school or technical secondary school and below	210		45.70 ± 6.10	44.09 ± 9.33[a]	27.98 ± 3.88[a]
	College or undergraduate	205		46.41 ± 7.43	47.44 ± 10.32[a]	26.39 ± 4.47[a]
	Postgraduate and above	63		46.17 ± 7.56	50.17 ± 10.84	25.57 ± 3.81
			F	0.558	11.250	11.890
			P value	0.573	< 0.001	< 0.001
Mother's educational background	High school or technical secondary school and below	221		46.26 ± 7.29	48.06 ± 10.09	26.54 ± 4.37
	College or undergraduate	203		46.76 ± 7.28	47.80 ± 10.04	26.44 ± 4.32
	Postgraduate and above	54		45.52 ± 6.94	50.39 ± 11.31	25.19 ± 3.85
			F	0.690	1.418	2.353
			P value	0.503	0.243	0.096
Family domicile	Village	208		46.40 ± 6.86	47.54 ± 9.75	26.72 ± 4.31
	County	117		46.25 ± 7.26	47.51 ± 10.67	26.34 ± 4.53
	Downtown	153		46.48 ± 7.76	49.67 ± 10.41	25.84 ± 4.07
			F	0.034	2.294	2.401
			P value	0.967	0.102	0.092
Average sleep time	< 6 h	83		48.02 ± 7.71	50.10 ± 9.63	25.46 ± 4.27
	6-8 h	257		46.02 ± 7.35	48.11 ± 10.21	26.54 ± 4.29

> 8 h	138		46.09 ± 6.65	47.28 ± 10.51	26.51 ± 4.31
		F	2.572	2.972	2.131
		P value	0.078	0.053	0.120

[a]*P* < 0.05, compared to the father's education level of postgraduate or above.
SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SES: the Self-Esteem Scale.

Table 4 Assignment table

Independent variables	Assignment
Gender	Male = 1; Female = 0
Only child	Yes = 1; No = 0
Major	Humanities and social sciences = 1; Science and engineering = 2; Medicine = 3
Father's educational background	High school or technical secondary school and below = 1; College or undergraduate = 2; Postgraduate and above = 3
Mother's educational background	High school or technical secondary school and below = 1; College or undergraduate = 2; Postgraduate and above = 3
Family domicile	Village = 1; County = 2; Downtown = 3
Average sleep time	Actual value
PARS-3 scores	Actual value

PARS-3: Physical Activity Rank Scale-3.

Table 5 Multivariate logistic regression for anxiety, depression, and low self-esteem

Model	Independent variables	Anxiety			Depression			Low self-esteem		
		B	*P* value	OR (95%CI)	B	*P* value	OR (95%CI)	B	*P* value	OR (95%CI)
1	PARS-3 scores	-0.065	< 0.001	0.937 (0.923-0.951)	-0.063	< 0.001	0.939 (0.926-0.952)	-0.077	< 0.001	0.926 (0.910-0.943)
	Constant	0.781	< 0.001	2.184	0.896	< 0.001	2.449	0.799	< 0.001	2.224
2	PARS-3 scores	-0.065	< 0.001	0.937 (0.923-0.951)	-0.063	< 0.001	0.939 (0.926-0.952)	-0.077	< 0.001	0.926 (0.910-0.943)
	Average sleep time	-0.064	0.236	0.938 (0.844-1.043)	-0.045	0.397	0.956 (0.862-1.061)	-0.005	0.931	0.995 (0.891-1.111)
	Constant	1.247	0.005	3.480	1.222	0.005	3.394	0.835	0.068	2.304
3	PARS-3 scores	-0.067	< 0.001	0.935 (0.921-0.949)	-0.064	< 0.001	0.938 (0.925-0.951)	-0.078	< 0.001	0.925 (0.908-0.942)
	Average sleep time	-0.083	0.134	0.921 (0.826-1.026)	-0.054	0.318	0.948 (0.853-1.053)	-0.012	0.835	0.988 (0.883-1.106)
	Gender	-0.145	0.540	0.865 (0.543-1.377)	-0.173	0.455	0.841 (0.535-1.324)	-0.055	0.825	0.947 (0.582-1.539)
	Only child	-0.360	0.132	0.698 (0.437-1.114)	-0.472	0.043	0.624 (0.395-0.986)	-0.136	0.585	0.873 (0.536-1.421)
	Major		0.020			0.132			0.174	
	Humanities and social sciences	0.137	0.631	1.147 (0.656-2.005)	0.382	0.164	1.465 (0.855-2.511)	0.397	0.182	1.488 (0.830-2.667)
	Science and engineering	0.769	0.007	2.158 (1.232-3.780)	0.542	0.055	1.719 (0.990-2.987)	0.533	0.076	1.704 (0.945-3.073)
	Father's educational background		0.454			0.924			0.669	
	High school or technical	-0.013	0.987	0.987 (0.202-	0.310	0.691	1.364 (0.296-	0.310	0.714	1.364 (0.260-

Secondary school and below			4.813)			6.284)			7.150)
College or undergraduate	0.440	0.555	1.553 (0.360-6.700)	0.255	0.722	1.291 (0.316-5.277)	0.557	0.476	1.745 (0.378-8.048)
Mother's educational background		0.685			0.776			0.325	
High school or technical secondary school and below	-0.165	0.830	0.848 (0.187-3.835)	-0.512	0.489	0.599 (0.140-2.559)	-1.175	0.141	0.309 (0.065-1.478)
College or undergraduate	0.176	0.833	1.193 (3.835-6.156)	-0.559	0.490	0.572 (0.117-2.797)	-1.002	0.250	0.367 (0.067-2.025)
Family domicile		0.448			0.939			0.613	
Village	0.036	0.915	1.037 (0.534-2.011)	-0.110	0.741	0.896 (0.467-1.719)	0.080	0.821	1.084 (0.541-2.173)
County	-0.330	0.360	0.719 (0.355-1.457)	-0.109	0.756	0.897 (0.451-1.782)	-0.230	0.543	0.795 (0.379-1.666)
Constant	1.263	0.031	3.538	1.627	0.005	5.087	1.322	0.029	3.753

Model 1 does not adjust for any variables; Model 2 adjusts the average daily sleep time; and Model 3 adjusts the average daily sleep time, gender, only child, major, father's educational background, mother's educational background, and family residence. PARS-3: Physical Activity Rank Scale-3.

Table 6 Receiver operating characteristic curve of Physical Activity Rank Scale-3 scores predicting anxiety, depression, and low self-esteem

Dependent variables	AUC	Sensitivity	Specificity	Standard error	*P* value
Anxiety	0.805 (0.760 -0.849)	0.799	0.743	0.023	< 0.001
Depression	0.799 (0.755-0.843)	0.801	0.716	0.022	< 0.001
Self-esteem	0.831 (0.788-0.874)	0.748	0.814	0.022	< 0.001

PARS-3: Physical Activity Rank Scale-3; AUC: Area under the curve.

Table 7 Correlation matrix between Physical Activity Rank Scale-3 scores and Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Self-Esteem Scale scores

Indexes		SAS	SDS	SES
PARS-3	*r*	-0.566	-0.621	0.621
	P value	< 0.001	< 0.001	< 0.001
SAS	*r*	-	0.511	-0.508
	P value	-	< 0.001	< 0.001
SDS	*r*	-	-	-0.518
	P value	-	-	< 0.001

PARS-3: Physical Activity Rank Scale-3; SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale; SES: the Self-Esteem Scale.

was associated with being more prone to depression, which was in line with extant studies[27]. College students with high self-esteem are confident, self-reliant, rational, and peaceful. Their self-evaluation is generally positive; they can rationally face the negative evaluation of others and effectively filter negative information. In addition, college students with high self-esteem have a better sense of control over their environment, can accept and adapt to the existing environment, and are willing to change themselves. When facing stressful events, they can effectively use their current social support to provide a buffer for themselves and reduce the negative impact of stressful events[28]. This effectively reduces the occurrence of anxiety and depression among college students. Therefore, individuals with high self-esteem can self-regulate their depression and solve general psychological problems under stressful conditions. The correlation scatter plot suggests that exercise significantly impacts anxiety, depression, and self-esteem. However, the goodness of fit

is low, indicating that exercise alone is not the sole factor affecting these aspects in college students. Ramón-Arbués *et al* [29] demonstrated that anxiety, depression, and self-esteem of college students were also related to Internet use, smoking, and insomnia.

Anxiety, depression, and low self-esteem are contemporary college students' main mental health problems. The detection rate of anxiety and depression in Chinese college students is rising. College students urgently need an intervention method that can effectively relieve their anxiety, depression, and low self-esteem. This study demonstrates that increasing physical activity decreases anxiety and depression thereby boosting self-esteem in college students. It indicates the value of incorporating appropriate physical activities for promoting college students' psychological well-being and development. Moreover, a significant correlation exists between anxiety, depression, and self-esteem. Low self-esteem can contribute to the development of anxiety and depression. Therefore, regardless of the specific psychological changes in anxiety, depression, and self-esteem, one must be vigilant to any abnormal psychological development. Due to the limited information collected in this study, it was impossible to investigate the correlation between the amount of physical activity and sedentary behavior, video time, and other behaviors, which needs to be supplemented by future studies with large samples. Moreover, this cross-sectional survey design introduces potential problems such as uncertain time sequencing, external factor interference, data quality impact, and potential factor uncertainty, making it challenging to establish causality. Therefore, other research methods such as randomized controlled studies should be employed in the future to verify the results of this study.

CONCLUSION

Physical activity decreases anxiety and depression and increases self-esteem among college students. Colleges and universities should promote active participation in sports and implement scientifically balanced exercise routines. This can alleviate anxiety and depression, improve self-esteem, and enhance the overall physical and mental well-being of college students, ultimately contributing to their holistic development.

ARTICLE HIGHLIGHTS

Research background

College students experience varying levels of anxiety, depression, and self-esteem. As this reflects the quality of education reform in China, the correlation between physical activity and students' anxiety, depression, and self-esteem must be explored.

Research motivation

This study aimed to identify the factors related to anxiety, depression, and self-esteem among college students, and provide guidelines for interventions. Considering the influence and adjustability of physical activity in students, we speculated that the amount of physical activity among college students may be related to anxiety, depression, and self-esteem.

Research objectives

To analyze the influence of physical activity on anxiety, depression, and self-esteem among college students.

Research methods

We investigated 478 first-year college students using the Physical Activity Rank Scale-3 (PARS-3), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Self-Esteem Scale (SES). A multivariate logistic regression model, receiver operating characteristic curve (ROC), area under the curve (AUC), and Spearman's correlation analysis were employed to determine the correlation between PARS-3 and SAS, SDS, and SES scores.

Research results

PARS-3 was negatively correlated with SAS and SDS scores (r = -0.190, -0.267, both P < 0.001) and positively correlated with SES scores (r = 0.313, P < 0.001). SES was negatively correlated with SAS and SDS scores (r = -0.125, P = 0.016; r = -0.143, P = 0.002).

Research conclusions

Physical activity was negatively correlated with anxiety and depression and positively correlated with self-esteem.

Research perspectives

Based on the multi-factor logistic regression model, ROC, AUC, and Spearman's correlation analysis, we comprehensively analyzed the correlation between college students' PARS-3 scores and SAS, SDS, and SES scores. We demonstrated that college students' PARS-3 scores were negatively correlated with SAS and SDS scores and positively correlated with SES scores. This could guide future interventions to reduce anxiety, depression, and low self-esteem among college students.

FOOTNOTES

Author contributions: Fu HY designed and conducted the research, and authored the paper; Wang J designed the research and supervised the report; Hu JX designed the research and contributed to the analysis.

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ORIGINAL ARTICLE

Observational Study

Influence of childhood trauma on adolescent internet addiction: The mediating roles of loneliness and negative coping styles

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Abstract

BACKGROUND

In the information age, the use of the internet and multimedia tools has large effects on the life of middle school students. Improper use of the internet may result in internet addiction (IA). Thus, actively exploring the factors influencing adolescent and the mechanism of addiction as well as promoting adolescent physical and mental health and academic development are priorities that families, schools, and society urgently need to address.

AIM

To explore the effect of childhood trauma on adolescent IA and to consider the roles of loneliness and negative coping styles.

METHODS

A total of 11310 students from six junior high schools in Henan, China, completed the child trauma questionnaire, IA test, loneliness scale, and simple coping style questionnaire. In addition, data were collected from 1044 adolescents with childhood trauma for analysis with IBM SPSS 26.0 and AMOS 28.0; we examined the relationships among childhood trauma, IA, loneliness, and negative coping styles.

RESULTS

We found that childhood trauma not only directly affected adolescents' IA but also affected IA through loneliness and negative coping styles.

CONCLUSION

Therefore, this study has theoretical implications regarding adolescent mental health and may inform interventions for IA.

Key Words: Addictive behavior; Mental health; Coping styles; Trauma; Loneliness

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Core Tip: This study is concluded: (1) Childhood trauma has a positive predictive effect on teenagers' internet addiction (IA); (2) Childhood trauma has a negative psychological and behavioral impact on teenagers; (3) Loneliness and negative coping styles play a chain intermediary role in the influence of childhood on IA among teenagers; and (4) IA.

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INTRODUCTION

In the information age, the use of the internet and multimedia tools has a large effect on the lives of middle school students. Improper use of the internet may result in internet addiction (IA). IA is often defined as problematic, compulsive internet use (for gaming, social networks, pornography, *etc.*) that results in severe impairment of an individual's functioning in all aspects of life over a long period[1,2]. Worldwide, the current prevalence rate of IA is 7.02%; alarmingly, the age of IA onset is dropping, and the prevalence rate is increasing[3]. From 2004 to 2019, a questionnaire survey of 92171 middle school students in Shanghai, China, reported that the prevalence rate of IA was 4.3%, that students with high levels of loneliness exhibited IA, and that academic pressure aggravated IA[4]. Studies have shown that IA causes mental health problems in individuals and impairs psychosocial functioning, such as an inability to concentrate for long periods, isolation, anxiety, social withdrawal, depression, interpersonal avoidance, and sleep disorders[5-8]. Physical health problems such as dry eye, mouse hand, and cervical and lumbar spine pain can also occur [9,10]. Moreover, some studies have shown that IA is related to non-suicidal self-injury and suicide in adolescents[11-13]. Thus, actively exploring the factors influencing adolescent IA and the mechanism of addiction as well as promoting adolescent physical and mental health and academic development are priorities that families, schools, and society urgently need to address.

Childhood trauma and IA

Childhood trauma is often described as serious adverse childhood experiences, mainly involving neglect and abuse[14], which have a series of negative effects on physical and mental health[15,16]. Unfortunately, childhood trauma is very common. According to Koenen *et al*[17], 38.48% of children have been exposed to at least one traumatic event before the age of 13. Childhood trauma is associated with the development of various addictive behaviors, which have become an increasingly serious public health problem[18-20]. For example, a study proved that childhood trauma is an important predictor of gambling disorder; physical neglect is the single trauma subtype that significantly increases the incidence of gambling disorder in adulthood[21]. It remains unclear whether childhood trauma is common among adolescents with IA. Therefore, we hypothesized that childhood trauma positively predicts adolescent IA (H1).

The potential mediating role of loneliness

Loneliness refers to complex feelings when the intimate relationship and social needs of individuals are not fully satisfied and are often accompanied by negative emotional experiences such as isolation, helplessness, and pain[22,23]. Abuse and neglect are severe childhood traumatic events and are lonely experiences. It is difficult for people without the same experience to truly understand these feelings. The traumatized person may have friends who support him or her, but because the friends cannot understand these feelings, the traumatized person may not be willing to share his or her experiences[24]. Therefore, even with the support of friends, they may feel lonely after the trauma. According to the social compensation hypothesis, lonely people may compensate for emotional or social needs through self-disclosure, self-catharsis, and interpersonal communication through the internet[25]. Adolescents with high levels of loneliness have a higher risk of IA[26,27]. However, it is unclear whether childhood trauma affects IA through loneliness. We hypothesized that loneliness influences the impact of childhood trauma on IA (H2).

The potential mediating role of negative coping styles

Coping styles are the cognitive and behavioral styles adopted by individuals in the face of setbacks and pressures. They are usually divided into positive coping styles (problem-solving, cognitive reassessment, social support, *etc.*) and negative coping styles (avoiding or denying problems or attributing solutions to external factors)[28,29]. Childhood is an important period of development, and traumatic experiences during this period will have a long-term impact on cognition and emotion regulation[30]. Some studies have shown that adolescents with childhood trauma mainly exhibit negative coping styles[31,32]. A reasonable explanation for using a negative coping style is that continuous exposure to childhood trauma

may lead to changes in one's neurobiology that lead to increased vigilance and perceived environmental threat, thus changing one's perceived stress[33]. Traumatic events will result in negative coping styles, which is consistent with the stress response model[34]. Some studies have indicated that addictive behaviors are closely related to the selected coping style, especially negative coping styles[35-37]. Adolescents may exhibit negative coping methods on the internet such as venting, avoiding, or denying difficulties encountered in reality[38]. Based on previous theories and studies, we propose that negative coping styles mediate the relationship between childhood trauma and IA (H3).

Moreover, some studies have shown that loneliness affects coping styles[39,40], and negative coping styles positively predict IA[41,42]. However, few studies have shown that negative coping styles play an intermediary role in the relationship between loneliness and IA. In this study, we proposed that negative coping styles may mediate between loneliness and IA, and loneliness and negative coping styles have a chain mediating role in the relationship between childhood trauma and IA (H4).

Study framework

Childhood trauma, IA, loneliness, and negative coping styles interact with each other. Nevertheless, it remains unclear how these variables interact to lead to IA in adolescents. In this study, we proposed the conceptual framework shown in Figure 1. From the perspective of adolescents, we discuss the influence of childhood trauma on IA and investigate the role of loneliness and negative coping styles to provide empirical support and guidance for related research and interventions for adolescent mental health.

MATERIALS AND METHODS

Data collection and ethical considerations

From May to June 2023, volunteers were recruited from six junior and senior high schools in Henan Province, China, using a convenient sampling method. The inclusion criteria were as follows: (1) Enrolled in secondary school; and (2) Provided informed consent and volunteered to participate in this study. The exclusion criterion was the failure to complete all of the questionnaires, regardless of reason. This study was approved by the Institutional Review Committee of Henan Provincial Key Laboratory of Psychology and Behavior (20230516001), and all participants signed informed consent forms.

Questionnaire

General demographic data: We collected sociodemographic information including gender, age, parental marital status, only-child status, left-behind child status, family residential location, and relationships with teachers and classmates.

Childhood trauma questionnaire: We used the childhood trauma questionnaire compiled by Bernstein *et al*[43] and revised by Zhao *et al*[44]. The questionnaire consists of 28 questions, of which 3 are validity items designed to detect false-negative trauma reports. The questionnaire assesses five dimensions of childhood maltreatment. Each question is answered on a Likert scale, from 1 "never correct" to 5 "often correct". A higher overall score indicates a greater severity of trauma. The Cronbach's α coefficient of this study scale was 0.817.

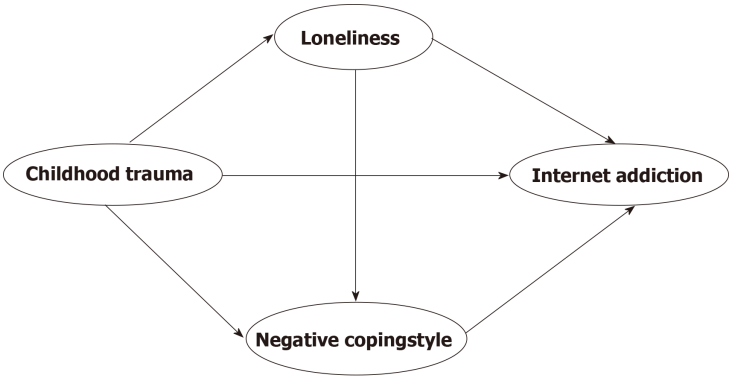
IA test: The IA test is a self-report scale compiled by young that contains 20 items[45]. Each entry is scored according to the degree of compliance on a scale of 1-5, and the total score range is 20-100 points. The higher the score is, the more severe the IA. A score ≥ 50 points indicates the presence of IA. The Cronbach's α coefficient was 0.909 in this study.

Loneliness scale: We used the University of California-Los Angeles Loneliness Scale compiled by Russell *et al*[46] in 1978. The scale consists of 20 items with 4 response options, 11 questions, and 9 reverse-scored questions. The higher the score is, the stronger the individual's experience of loneliness. The Cronbach's α coefficient in this study was 0.815.

Coping styles scale: Coping styles were evaluated with the simple coping style questionnaire, which was compiled by Xie[47] based on the Chinese context. It consists of two dimensions, positive response, and negative response, with a total of 20 items. Items are rated on a 4-point Likert scale (1 = not used, 4 = frequently used). This study focused on the negative response scale, which consists of 8 items and focuses on the characteristics of negative responses. The scale in this study had a Cronbach's α coefficient of 0.728.

Statistical analysis

All data were analyzed using IBM SPSS 26.0 and Amos 28.0 in this study. First, the frequency and percentage are reported for the demographic characteristics of participants. In addition, we used Harman's single-factor test to test for possible common method deviations. Normality tests were performed on continuous variables to detect skewness and kurtosis. If IA, loneliness, childhood trauma, and negative coping styles followed a normal distribution, we used Pearson's correlation analysis to explore the relationships among these variables. Otherwise, we used Spearman correlation analysis. We then used structural equation modeling to examine the mediation effects. In this study, IA was the dependent variable, childhood trauma was the independent variable, and loneliness and negative coping styles were the mediating variables. Based on previous item parceling studies[48], we used a "project-building balance" approach to package entries on loneliness and coping styles. Finally, bootstrapping was used to test the mediation effect, and if $P < 0.05$, the mediation effect was considered significant.



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Figure 1 Conceptual framework.

RESULTS

Sample results

We recruited a total of 11310 participants. Of these, 190 dropped out halfway and 11120 questionnaires were returned. After excluding questionnaires with incomplete data, we finally obtained 10819 valid questionnaires. Then, 9775 false-negative trauma reports were excluded. Finally, we analyzed the data of 1044 adolescents with childhood trauma, constituting 9.3% of the total number of participants in the survey, as shown in Figure 2. Bentler and Chou[49] proposed that the sample size should be more than 10 times the number of observed variables; therefore, 1044 samples met the requirements for testing the hypothesized model.

The demographic characteristics of the 1044 adolescents are shown in Table 1. Among them, 612 were male (58.6%), and 432 were female (41.4%). The students were in junior high school or high school, and the age range was 12-18 years. Among the sample, 937 were from two-parent families, and 105 were from single-parent families. A total of 70 (6.7%) students were only children, and the remaining 89.8% had siblings. In this survey, there were 458 (43.9%) left-behind children (students living with their grandparents, attending boarding school, or living alone), and there were 586 (56.1%) children living with their parents. Of these children, 56.6% were from rural areas, and the remaining 43.4% were from urban areas. A total of 48.8% of the students reported that they had a good relationship with their classmates, and 31.5% of the students reported that they had a good relationship with their teachers.

Bias test of common method

Because all data were collected with questionnaires, we used Harman's single-factor test to test for possible common method bias. The test results showed that there were 19 variables with eigenvalues greater than 1. The first variable explained 14.85% of the total variation, which is below the critical standard of 40%[50]. Hence, there were no serious common methodological biases in this study.

Descriptive statistics and correlations among variables

SPSS was used to examine the distributions of these variables, and all continuous variables had normal distributions. Therefore, we used Pearson correlation analysis to assess the correlations between variables. Means, standard deviations, and Pearson correlation coefficients of each variable are shown in Table 2. In this exploratory analysis, correlations between variables were examined with Pearson correlation analysis; there were significant correlations between each variable in this analysis at the significance level of 99%. Regarding the correlation coefficients, the r values were greater than 0. Thus, there was a significant positive correlation between the four dimensions of childhood trauma and each variable. The independent-sample t test results showed that there was a significant influence of parental marital relationship on IA (t = -4.252, P < 0.001). One-way ANOVA was used for variables with homogeneity of variance. The results showed that there were significant differences in IA among different ages (F = 16.86, P < 0.001). In addition, there were significant differences in IA according to relationships with peers and teachers (F = 9.837, P < 0.001). Considering that parent martial relationship (harmonious/disharmonious), age (12-18 years old), and relationship with teachers (poor/average/good) may influence IA, we decided to control for these variables in the subsequent mediation analysis.

SEM of factors influencing IA

Parents' marital relationship, age, and relationship with teachers were selected control variables because IA is significantly affected by these three variables. The model fit results are shown in Table 3; in accordance with Hu and Bentler [51], we provide several representative model fit indices. The CMIN/DF value of the model (4.616) was less than 5. The root mean square error of approximation value (0.059) was less than 0.08, and the root mean square residual value (0.040) was less than 0.05. In addition, the comparative fit index and goodness of fit index test results indicated excellent fit (0.9 or more). Therefore, the results of this analysis show that the SEM of factors influencing IA was satisfactory.

Table 1 Sample characteristics (*n* = 1044)

Variable	Option	*n*	*n*
Gender	Male	612	58.6
	Female	432	41.4
Age	12	16	1.5
	13	156	14.9
	14	175	16.8
	15	135	12.9
	16	286	27.4
	17	227	21.7
	18	49	4.7
Structure	Single parent	105	10.1
	Parents	937	89.8
Only child	Yes	70	6.7
	No	969	92.8
Stay-at-home children	Yes	458	43.9
	No	586	56.1
Residence	Village	591	56.6
	Town	449	43.4
Relationship with classmates	Poor	28	2.7
	General	506	48.5
	Good	509	48.8
Relationship with teachers	Poor	52	5.0
	General	662	63.4
	Good	329	31.5

Table 2 Correlations of variables and mean ± SD

Variables	mean ± SD	EN	PaEB	SB	BN	NCS	Loneliness	IA
EN	2.37 ± 0.85	1						
PaEB	1.44 ± 0.44	0.509[a]	1					
SB	1.17 ± 0.43	0.098[a]	0.273[a]	1				
BN	1.5 ± 0.47	0.293[a]	0.449[a]	0.252[a]	1			
NCS	2.22 ± 0.58	0.092[a]	0.217[a]	0.212[a]	0.263[a]	1		
Loneliness	2.26 ± 0.47	0.347[a]	0.336[a]	0.108[a]	0.258[a]	0.246[a]	1	
IA	2.43 ± 0.43	0.154[a]	0.254[a]	0.167[a]	0.307[a]	0.379[a]	0.334[a]	1

[a]$P < 0.01$.

EN: Emotional neglect; PaEB: Physical and emotional abuse; SB: Sexual abuse; BN: Body neglect; NCS: Negative coping style; IA: Internet addiction.

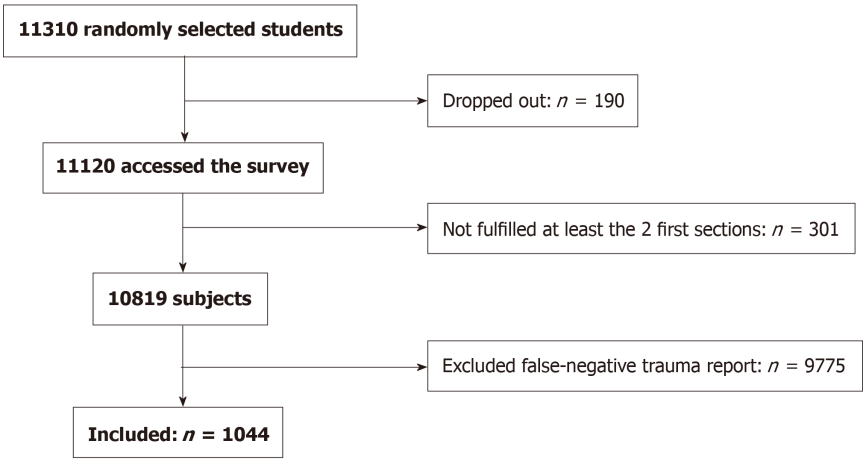
Factors hypothesized to influence IA

According to the results shown in Figure 3, childhood trauma positively predicted loneliness ($\beta = 0.50$, $P < 0.001$), childhood trauma positively predicted negative coping style ($\beta = 0.25$, $P < 0.001$), loneliness positively predicted negative coping style ($\beta = 0.21$, $P < 0.001$), loneliness positively predicted IA ($\beta = 0.14$, $P < 0.001$), negative coping style positively predicted IA ($\beta = 0.30$, $P < 0.001$), and childhood trauma positively predicted IA ($\beta = 0.17$, $P < 0.001$).

Table 3 Model fit test

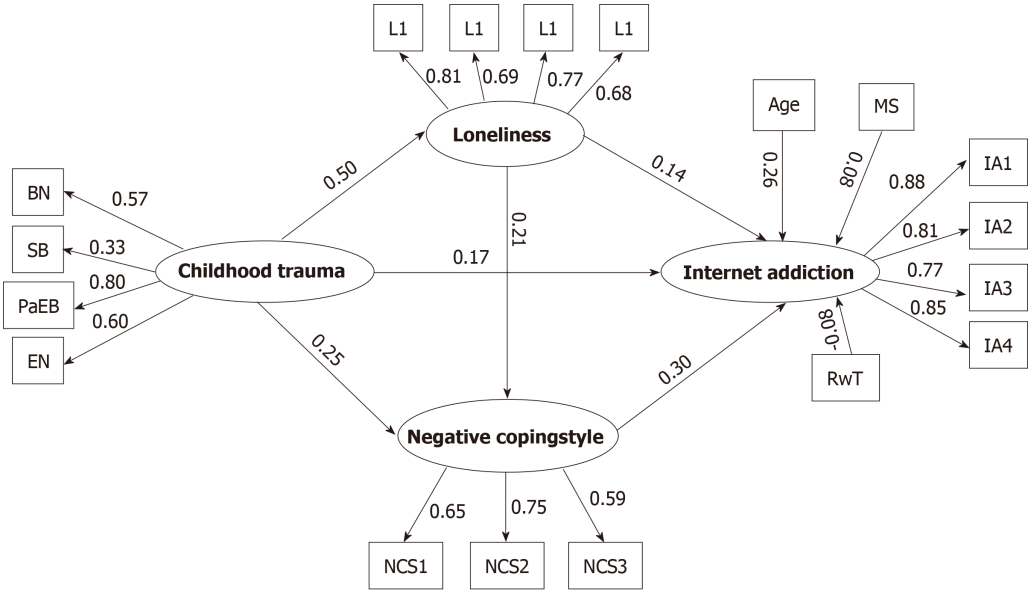
Model	CMIN/DF	RMSEA	RMR	CFI	GFI
Childhood trauma and loneliness and negative coping styles and IA	4.616	0.059	0.040	0.926	0.937
Fitting standard	< 5	< 0.08	< 0.05	> 0.90	> 0.90

RMSEA: Root mean square error of approximation; RMR: Root mean square residual; CFI: Comparative fit index; GFI: Goodness of fit index; IA: Internet addiction.



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Figure 2 Flow diagram of participants.



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Figure 3 The SEM of factors influencing internet addiction. EN: Emotional neglect; PaEB: Physical and emotional abuse; SB: Sexual abuse; BN: Body neglect; L1-L4: Four items of loneliness; IA1: Tolerability and time management; IA2: Compulsivity and prominence; IA3: Interpersonal, study and health; IA4: Abstinence reaction; NCS1-NCS3: Three items of negative coping style; MS: Marital status; RwT: Relationship with teachers.

Finally, we used 5000 bootstrap samples to determine the 95% confidence interval, and assessed the mediating effects of loneliness and negative coping style on the relationship between childhood trauma and IA. The results are shown in Table 4; loneliness mediated in the relationship between childhood trauma and IA. Negative coping styles also mediated the relationship between childhood trauma and IA. In addition, loneliness and negative coping styles had a chain mediating role in the relationship between childhood trauma and IA. In short, childhood trauma not only directly affected IA but also indirectly affected IA through loneliness and negative coping style in a chain mediation effect

Table 4 Structural equation modeling results

Effect	Path	Estimate	*P* value
Ind2	IA < loneliness < childhood trauma	0.093	0.005
Ind2	IA < negative coping style < childhood trauma	0.104	0.001
Ind3	IA < negative coping style < loneliness < childhood trauma	0.044	0.001
Direct	IA < childhood trauma	0.241	0.001
Total	IA < childhood trauma	0.476	0.001

IA: Internet addiction.

(Table 4).

DISCUSSION

Among the 1044 adolescents with childhood trauma, there were 473 (45.6%) students with IA, and the prevalence rate was as high as 45.6%, which is higher than the Hu *et al*[52] reported. Among these participants, 75 had severe IA. This may be related to the unique study population (adolescents with childhood trauma). We explored the relationship between childhood trauma and IA in adolescents. The mediating roles of loneliness and negative coping styles were determined through a chain mediation model. To address IA in adolescents with childhood trauma, it is of practical and theoretical importance to study the relationships among these variables.

Childhood trauma and IA

The results of this study revealed a direct relationship between childhood trauma and IA, suggesting that physical and emotional neglect/abuse in childhood are important predictors of adolescent IA, which is consistent with previous findings and supports H1. Studies have shown that childhood trauma can lead to poor behavior in adolescents[53,54]. For example, childhood trauma can directly predict adolescent mobile phone addiction as well as IA[55,56]. The present study showed that childhood trauma is significantly associated with IA, which is consistent with previous research results[57]. Importantly, this study also showed that adolescents with IA accounted for 45.6% of the sample, which differs from previous findings, suggesting that adolescents with childhood trauma are more likely to have IA. Traumatic childhood experiences have various adverse effects on adolescents in physical, psychological, emotional, and behavioral dimensions. Studies have shown that children who have experienced childhood trauma are often in a clinical or subclinical psychological state, and they will be more inclined to use the internet to express their sadness, depression, and other psychological states and obtain comfort[58]. Thus, we should pay attention not only to the health and academic needs of adolescents but also to their psychological and emotional needs. School-based health care centers and education systems are key resources for adolescent trauma interventions. Schools can identify students with childhood trauma through screening, focusing on their health. This will be more conducive to adolescents' healthy growth and reduce problem behaviors such as IA.

Mediation through loneliness

This study explored the mechanism underlying the association between childhood trauma and adolescent IA and showed that loneliness plays a mediating role in this relationship, supporting hypothesis 2. The results showed that childhood trauma significantly predicted adolescent loneliness, which is consistent with previous studies[59,60]. Loneliness is a common experience in adolescence. According to a survey, 11%-20% of those aged 12-15 years reported that they felt lonely at least "sometimes"[61]. Childhood trauma aggravates adolescents' depression and inferiority complexes, limits their social communication, and thus aggravates loneliness. Moreover, loneliness is a negative emotional state and is closely related to some mental disorders. For example, loneliness and depression are associated[62]. This study showed that loneliness has an impact on adolescent IA, which is consistent with previous research results[63]. Adolescents with high levels of loneliness tend to use the internet instead of offline social interactions to meet the need to belong[64]. However, IA aggravates the loneliness of adolescents. Therefore, we suggest that schools organize more recreational activities for spare time to meet the social needs of adolescents. We should also prioritize the identification of students with communication barriers, emphasize the restoration of interpersonal relationships with time, help students actively integrate into the community, and prevent or reduce adolescent loneliness.

Mediating effect of negative coping styles

This study showed that negative coping styles have a mediating role in the effects of childhood trauma on IA, supporting hypothesis 3. The family risk factor model suggests that living in abusive or neglectful family environments can exacerbate or impose risks of poor self-perception, negative emotions, and coping styles as they adapt to social environments[65,66]. The results of this study are consistent with the family risk model, showing that childhood trauma positively predicts negative coping styles. Coping styles play an important role as mediating variables in an individual's

stress process[67-69]. Positive coping styles are conducive to regulating negative emotions when facing difficulty. In contrast, individuals with negative coping styles are more likely to choose to avoid difficulties. The results of this study also showed that negative coping styles positively predict adolescent IA behavior, which is consistent with previous studies[70]. However, IA can lead to additional stressful events, increased mental health problems, and decreased academic performance. Therefore, negative coping styles and IA form a negative cycle. At schools, we should guide adolescents to select positive and healthy coping styles, which are highly important for preventing or reducing adolescent IA.

Chain mediating effect of loneliness and negative coping styles

This study also indicated that loneliness can positively predict negative coping styles, which is consistent with previous studies[39,71]. In addition, we found that loneliness and negative coping style act as chain mediators of the relationship between childhood trauma and IA, supporting hypothesis 4. Adolescents with childhood trauma will inevitably have some negative emotions[72-74]. The coping style selected reflects the emotion regulation strategies of adolescents facing difficulty. Adolescents with negative coping styles tend to internalize their emotions with self-blame and avoidance. Engaging in internet use is a way of venting after trauma. Previous studies have shown that high levels of loneliness and negative coping styles are more likely to produce IA problems[75,76]. Overall, childhood trauma can predict loneliness, and loneliness can predict IA by influencing negative coping styles. Importantly, loneliness and coping styles can be changed. We can formulate intervention measures focusing on alleviating loneliness and cultivating positive coping styles, especially among adolescents with childhood trauma. We can help students enhance their mental health and psychological adjustment, develop a healthier and positive coping style, learn to reduce loneliness, and reduce the occurrence of IA among adolescents.

Limitations

First, this study investigated only six schools in one province, which somewhat reduces the generalizability of the conclusions. A study with a nationally representative sample and a multicenter design is needed. Second, this study used self-report data, which may have some problems, such as recall bias. Although no common method bias was found in this study, more objective assessments should also be considered in subsequent studies. Finally, this study had a cross-sectional design, and further longitudinal studies are needed to investigate causality.

CONCLUSION

This study constructed a chain mediation model from the perspective of adolescents to explore the process and mechanisms by which childhood trauma influences IA. Childhood trauma had a positive predictive effect on adolescent IA, and loneliness and negative coping styles had a chain mediating role in the influence of childhood on IA among adolescents. The path of childhood trauma® loneliness® negative coping styles® IA in adolescents was confirmed. This study provides empirical support and guidance for research and interventions for adolescent IA. In addition, it provides important insights into the mental health of middle school and the development of harmonious school life.

ARTICLE HIGHLIGHTS

Research background

Internet addiction (IA) refers to a compulsive or excessive use of the internet that interferes with daily life activities, relationships, and overall well-being. It is characterized by an individual's inability to control or limit their online behavior, leading to negative consequences.

Research motivation

This study aimed to explore the effect of childhood trauma on adolescent IA and to consider the roles of loneliness and negative coping styles.

Research objectives

The study hypothesized that childhood trauma would be positively associated with adolescent IA, and this relationship would be partially mediated by loneliness and negative coping styles. Negative coping styles refer to maladaptive strategies used to deal with stress, such as avoidance, substance use, and self-blame.

Research methods

This study constructed a chain mediation model from the perspective of adolescents to explore the process and mechanisms by which childhood trauma influences IA. Childhood trauma had a positive predictive effect on adolescent IA, and loneliness and negative coping styles had a chain mediating role in the influence of childhood on IA among adolescents.

Research results

The results showed that childhood trauma was positively associated with both loneliness and negative coping styles. Moreover, loneliness and negative coping styles were found to mediate the relationship between childhood trauma and adolescent IA. The findings suggest the importance of addressing childhood trauma and its subsequent impact on mental health and addictive behaviors.

Research conclusions

This study provides empirical support and guidance for research and interventions for adolescent IA, and it also provides important insights into the mental health of middle school and the development of harmonious school life.

Research perspectives

This study used self-report data, which may have some problems, such as recall bias. Although no common method bias was found in this study, more objective assessments should also be considered in subsequent studies.

FOOTNOTES

Co-first authors: Wang-Lin Dong and Yuan-Yuan Li.

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